

SCHMIDT
ORGANIC CHEMISTRY

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A TEXT-BOOK OF ORGANIC CHEMISTRY

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LIST OF ABBREVIATIONS

ABBREVIATIONS

JOURNALS

Acta Cryst	Acta Crystallographica.
Am. C. J.	American Chemical Journal.
Ann.	Liebig's Annalen der Chemie.
Ann. Chim. Phys. . . .	Annales de Chimie et de Physique.
Ann. Reports	Annual Reports of the Chemical Society.
Ann. Rev. Biochem. . .	Annual Review of Biochemistry.
Arch. Pharm.	Archiv. der Pharmazie.
Ber.	Berichte der deutschen chemischen Gesellschaft.
Biochem. J.	Biochemical Journal.
Biochem. Zeitsch. . . .	Biochemische Zeitschrift.
Biochem. Z.	Biochemische Zeitung.
Bull. Soc.	Bulletin de la Société Chimique.
C.	Chemisches Zentralblatt.
Chem. and Ind.	Chemistry and Industry.
Chem. Rev.	Chemical Reviews.
C. r.	Comptes rendus de l'Académie des Sciences.
Gazz.	Gazzetta Chimica Italiana.
Helv. Chim. Acta . . .	Helvetica Chimica Acta.
Ind Eng. Chem.	Journal of Industrial and Engineering Chemistry.
Ind. Eng. Chem. (Anal.)	Journal of Industrial and Engineering Chemistry. Analytical Edition.
J.A.C.S.	Journal of the American Chemical Society.
J. Biol. Chem.	Journal of Biological Chemistry.
J.	Journal of the Chemical Society.
J. Chem. Ed.	Journal of Chemical Education.
J. Org. Chem.	Journal of Organic Chemistry.
J. Physiol.	Journal of Physiology.
J. Phys. Chem.	Journal of Physical Chemistry.
J. pr. Ch.	Journal für praktische Chemie.
J.S.C.I.	Journal of the Society of Chemical Industry.
Monats.	Monatshefte für Chemie.
Proc. Chem. Soc. . . .	Proceedings of the Chemical Society.
Proc. Roy. Soc.	Proceedings of the Royal Society.
Quart Reviews	Quarterly Reviews of the Chemical Society.
Rec. trav. chim.	Recueil des travaux chimiques des Pays-bas.
Trans. Farad. Soc. . . .	Transactions of the Faraday Society.
Z. anal. Ch.	Zeitschrift für analytische Chemie.
Z. ang. Ch.	Zeitschrift für angewandte Chemie.
Z. Elek.	Zeitschrift für Elektrochemie.
Z. Krist.	Zeitschrift für Kristallographie.
Z. phys. Ch.	Zeitschrift für physikalische Chemie.
Z. physiol. Ch.	Zeitschrift für physiologische Chemie.

ORGANIC CHEMISTRY

Introduction

COMPARATIVELY early in the history of chemistry an interest began to be taken in the remarkable variety of carbon compounds which could be prepared from plant and animal sources. This led eventually to systematic investigations on their origin and the manner in which they could be transformed one into another. It was not until the eighteenth century, however, that the first results of importance were obtained at the hands of Lavoisier. The work was found to present peculiar difficulties and to require a special laboratory technique, hence at the beginning of the nineteenth century it was severed completely from inorganic chemistry and considered as a separate branch of chemical science. The name of *Organic Chemistry* originated in the belief that compounds of this type could not be prepared artificially in the laboratory, but were formed solely in living organisms under the influence of a mysterious agency termed Vital Force. Experimental evidence at first lent support to this theory, in so far that all attempts to build up such substances from materials not themselves obtained from living organisms were unsuccessful.

The Vital Force theory was disproved by the syntheses of organic compounds from inorganic constituents. It is often stated that the theory was discarded as the result of Wöhler's discovery¹ in 1828 that urea, one of the most characteristic products of animal metabolism, could be prepared from the inorganic constituents cyanic acid and ammonia. It has been pointed out, however, that the cyanic acid was obtained from organic matter such as dried blood and therefore could not be termed inorganic.² Since that time a large number of organic compounds have been synthesised from purely inorganic materials, one of the earliest being that of Kolbe,³ who in 1845 prepared acetic acid from carbon disulphide.

Other syntheses followed, until it was proved beyond all doubt that the same chemical forces operated in the organic as in the inorganic world, and the assumption of a vital force responsible for the production of carbon compounds in the organism was therefore superfluous. Nevertheless there are many substances of plant and animal origin, including

¹ Wöhler, "Ueber künstliche Bildung des Harnstoffs," *Pogg. Ann.*, 1828, 22. ² See J. Read, *Text-Book of Organic Chemistry*, p. 146; Douglas McKie, *Nature*, 1944, 153, 608.
³ *Ann.*, 1845, 54, 145.

the very widespread class of proteins, which have so far eluded artificial preparation. Various reasons may be put forward to explain this lack of success. Not only has the precise chemical composition of the proteins yet to be determined, but even the mode of union of the atoms in these compounds is still uncertain. Nor have we any clear conception of the physico-chemical conditions under which these substances are produced in the living organism.

Although we still speak of organic and inorganic chemistry, the terms are retained solely for convenience of reference. The peculiarities of organic compounds depend only on the nature of their principal constituent carbon, and the wide extent of organic chemistry is a direct consequence of the unique combining capacity of the carbon atom. No other element approaches carbon in its ability to unite with itself, atom by atom, to form open and closed chains, and as a result, the number of known carbon compounds, now well over 500,000, exceeds that of the compounds of all the other elements put together.

*Organic Chemistry is thus to be defined as the chemistry of carbon compounds.*¹

As the majority of organic compounds resulting from plant and animal activity consist only of carbon, hydrogen, oxygen and less frequently nitrogen, these elements have been termed organogenetic. Organic substances containing sulphur, phosphorus and more rarely other elements are also known to occur in nature, but their number is relatively small. On the other hand, by artificial means it is possible to prepare organic derivatives of any of the elements except the rare gases.

ANALYSIS OF ORGANIC COMPOUNDS

Relatively few organic compounds are distinguished by reactions sufficiently characteristic to serve as a basis for their qualitative identification. For the separation of organic substances from mixtures there is therefore no general procedure known comparable to the systematic analysis of inorganic chemistry.

In many cases the physical properties of a substance such as smell, crystalline form, melting-point, boiling-point, or optical rotation enable it to be identified. More often it is necessary to determine its composition, first qualitatively and then quantitatively.

Methods for the qualitative and quantitative determination of carbon, hydrogen, nitrogen, halogens, etc., will be found in books on practical organic chemistry. Microanalysis of organic compounds is now widely employed, a few milligrammes of a compound being sufficient for its complete analysis.²

¹ Carbon itself and a few of its simple compounds, such as carbon dioxide and carbonates which are of frequent occurrence in the mineral world, are usually described in text-books on inorganic chemistry and are not included here ² F. Pregl, *Quantitative Organic Analysis*, translated by E. Fyfe (Churchill)

CALCULATION OF EMPIRICAL FORMULÆ

The formula of the substance is deduced from the percentage composition, as found by analysis, in the same way as with inorganic compounds. The percentage figures are first divided by the atomic weights of the elements to which they have reference; the quotients thus obtained show the relative proportions in which the atoms are combined together. On using the smallest of these quotients as a divisor for the others, values are arrived at which either approximate to whole numbers or do so after further simple multiplication. The formula finally deduced should be in accordance with the Law of Even Numbers.

Example.—The analysis of a substance consisting of carbon, hydrogen, nitrogen, chlorine and oxygen gave

	44·05% C,	7·31% H,	10·18% N,	26·19% Cl,	and by difference 12·20% O.
The divisions	$\frac{44\cdot05}{12},$	$\frac{7\cdot31}{1},$	$\frac{10\cdot18}{14},$	$\frac{26\cdot19}{35\cdot5},$	$\frac{12\cdot20}{16}$ yield the
figures	3·67,	7·31,	0·73,	0·74,	0·76
These divided by 0·73 give	5·02,	10·01,	1·0,	1·01,	1·04

From which the simplest formula is $C_5H_{10}ONCl$.

The simplest formula obtained in this way is termed the *empirical formula*, and does not always correspond to the real molecular weight, which may prove to be some higher multiple thereof.

After discovering the percentage composition of a substance and with it the proportions in which the atoms are united together, the next problem is to ascertain the true molecular weight.

DETERMINATION OF MOLECULAR WEIGHT—MOLECULAR FORMULA OF AN ORGANIC COMPOUND

It is frequently possible to deduce the probable molecular weight of a compound from the reactions by which it is formed. In other cases the information can be gained from a detailed chemical investigation of the nature of the substance. In most instances, however, the best results are given by physical methods.

Determination of Molecular Weight by Chemical Methods

It should be said at once that an absolutely sure method of determining molecular weights by purely chemical means is not available. It is only possible to eliminate certain of the values in question and to estimate with some probability the actual size of the molecule.

For this purpose derivatives of the substance must be prepared possessing an atom or radical capable of being quantitatively determined, from the proportion of which the molecular formula of the derivative may be calculated and hence that of the parent substance.

which combines with 36.4 gms. HCl, and may be calculated from the chlorine content of aniline hydrochloride. On precipitation with silver nitrate, 0.2590 gm. of this salt gives 0.2870 gm. of silver chloride, which corresponds to 0.073 gm. of HCl. Consequently 0.259 gm. of the salt contains 0.073 gm. of HCl, and by difference 0.186 gm. of aniline. From this it follows from the equation

$$0.073 : 0.186 = 36.4 : x$$

that 93 parts by weight of aniline are united with 36.4 parts of HCl.

The empirical formula C_6H_5N also gives 93 as the molecular weight and is therefore to be considered as the molecular formula of aniline.

Example III.—Caffeine, the physiologically active constituent of coffee and tea, gives on analysis the empirical formula $C_4H_5N_2O$.

It is a monacid base, and its platinum compound consists therefore of 2 mols. of caffeine combined with 2 mols. of hydrochloric acid and 1 mol. of platinum chloride. On ignition 100 parts by weight of this compound give 24.6 parts of metallic platinum; consequently the weight containing one atomic proportion (194.8) of platinum is

$$\frac{194.8 \times 100}{24.6} = 791.8.$$

These 791.8 parts of the platinum double salt consist however of 2 mols. of caffeine combined with $2HCl + PtCl_4$; the molecular weight of caffeine is therefore obtained from the equation

$$2x + (2 \times 36.4) + 336.3 = 791.8 \\ x = 191.$$

The formula $C_4H_5N_2O$ quoted above, corresponding to the mol. wt. 97, must therefore be doubled, giving the molecular formula of caffeine as $C_8H_{10}N_4O_2$.

The majority of organic compounds are neither acids nor bases, and with indifferent substances such as these it is frequently impossible to determine the molecular weight by purely chemical methods. Sometimes a detailed study of the reactions of the substance leads to a definite conclusion.

Investigation may be made, for example, as to the manner in which the compound behaves on the substitution of hydrogen by chlorine, and the proportion of the total hydrogen which is replaceable in this way.

Example I.—Chloro-substituted carboxylic acids can be prepared by the direct action of chlorine on the acids. Acetic acid, with the empirical formula CH_3O , gives according to experimental conditions three different acids on treatment with chlorine, the final product of substitution having the formula $C_2HO_2Cl_3$. In acetic acid itself there are therefore three hydrogen atoms replaceable by chlorine, pointing to the molecular formula $C_2H_4O_2$ for acetic acid.

Example II.—The simplest formula for naphthalene as deduced from analytical data is $C_{10}H_8$. Naphthalene reacts with chlorine, however, to give a substance, monochloronaphthalene, containing 73.8 per cent. C, 4.3 per cent. H and 21.9 per cent. Cl, from which the formula $C_{10}H_7Cl$ is derived. This compound is produced from naphthalene by the substitution of hydrogen by chlorine, so that at least one whole atom must have been replaced, since fractions are excluded. From the formula $C_{10}H_7Cl$, therefore, it is obvious that at least $\frac{1}{2}$ of the total hydrogen in the original compound has been replaced, and naphthalene contains in consequence 8, or 2×4 , or 3×3 , etc., hydrogen atoms, together with 10 (or a multiple of 10) carbon atoms. A multiple of 8 or 10 is, however, out of the question, since no derivatives have ever been obtained

from naphthalene indicating the possibility of replacing, for example, $\frac{1}{2}$ or $\frac{1}{3}$ of the total hydrogen. For these reasons the formula C_6H_4 is doubled, and the molecular formula $C_{10}H_8$ assumed for naphthalene.

Determination of Molecular Weight by Physical Methods¹

Of the many processes available for this purpose, those which have proved of greatest service to the organic chemist are the determination of molecular weight by measuring the elevation of boiling-point or the depression of freezing-point of a solution. These are described in full detail in analytical text-books.

Polymerism

It is seen from the foregoing pages that compounds of the same percentage composition may possess different molecular weights and therefore different properties. Such compounds are said to be **polymers** or **polymerides**. The number of organic compounds exhibiting this relationship is very large, familiar examples being cyanic acid, $HCNO$, and cyanuric acid, $(HCNO)_3$; formaldehyde, CH_2O , and fructose, $C_6H_{12}O_6$.

Molecular Structure and Isomerism

Even supposing the composition and molecular weight of a substance to have been determined by means of the methods indicated in the previous chapter, the molecular formula arrived at from these data is not yet sufficiently characteristic to obviate the possibility of confusion with other substances. There are numerous organic compounds of the same percentage composition and molecular weight which nevertheless differ in their physical and chemical properties. Such substances are called **isomers**, or **isomerides**.

For example, five different compounds are known having the composition and molecular formula C_3H_8O , and ethylamine and dimethylamine of the same molecular formula C_2H_7N show considerable differences in their chemical and physical behaviour.

The reason for such differences must be sought in the internal structure of the molecules, which are assumed to contain a dissimilar *arrangement* of atoms. This difference of arrangement may refer :—

(a) To the manner in which the atoms are linked together, without reference to their positions in space. These are cases of **structural isomerism**, and are treated in detail under the theory of structure.

(b) To the relative position of the atoms in space. These are cases of **stereoisomerism** and are discussed under stereochemistry.

It is a point of interest that the development of these two branches, which together comprise the theory of molecular structure, originated solely in the sphere of organic chemistry.

¹ Two simple micro-methods of determining molecular weights have been described by G. Barger (*J.*, 1904, 85, 286; see also K. Rast, *Ber.*, 1921, 54, 1979) and by K. Rast, *Ber.*, 1922, 55, 1051.

VALENCY

I.—STRUCTURE

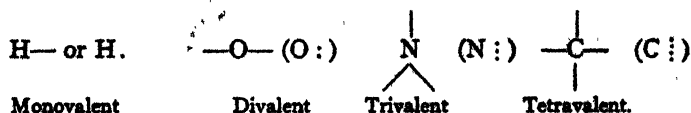
The theory of the structure of organic compounds deals with the manner in which the atoms are connected one with another, and is based on the conception of valency.

(a) Outline of the Theory of Valency

In the year 1858 Kekulé advanced two hypotheses which form the foundation of modern views on the structure of carbon compounds. They postulated that carbon is a tetravalent element and that its atoms have the power to combine one with another.¹ Somewhat later Couper² published similar views, which gave rise to the idea of atomic linkings.³

Whereas at first it was assumed that the different atoms forming a molecule were held together in such a manner that one attracted all or a certain number of the others, and these themselves exerted a reciprocal attraction on the first, thus holding it in position, it was realised later that this mutual influence extended only from atom to atom. Graphically expressed, the atoms are conceived as strung into a chain, each member being linked to those adjacent to it; if one be removed and not replaced by another, the chain breaks and the compound decomposes. Such chains may be built up from a variety of atoms which need not be of the same valency. A monovalent atom such as hydrogen, however, has only the one opportunity of union, whilst one which is divalent has two, and so on.

The power of union or valency of an atom is indicated by placing small lines or points close to the symbols of the elements, in such a way that each line or point expresses a unit of valency :



Assuming that in the formation of a compound these valencies are mutually used up, it follows that those elements which combine with hydrogen according to the formula X—H must, like hydrogen, be monovalent. The elements which combine according to the formulae



are then di-, tri- and tetravalent respectively.

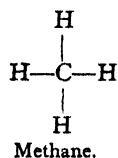
The further development of the theory of valency in inorganic chemistry is complicated by the fact that elements do not always exhibit the same valency; thus copper is mono- or divalent according to whether it is present in a cuprous or a cupric compound. In organic chemistry the

¹ *Ann.*, 1858, 206, 151. ² *Ann. chim. phys.*, 1858 (3), 53, 469. ³ It should be noted that Kekulé and Couper are not the actual founders of the theory of valency. This honour belonged to Frankland and Kolbe. The former investigators have, however, rendered the great service of expanding the ideas of Frankland and Kolbe, and of applying them to organic chemistry.

conditions are simpler, since the elements H, O, and C, of which the majority of important carbon compounds are composed, show with comparatively few exceptions a constant valency. In other words, hydrogen is monovalent, oxygen generally divalent¹ and carbon tetravalent.

The manner in which the atoms are linked up within the molecule indicates the constitution or structure of the compound, and is expressed by means of constitutional or structural formulæ. These are built up according to the following rules, based on experience :—

1. *The carbon atom is usually tetravalent*, in agreement with its position in the periodic classification. A carbon atom may thus combine with a maximum of four monovalent atoms or groups. This is illustrated by one of the simplest organic compounds, marsh gas or methane, in which one atom of carbon is combined with four atoms of hydrogen.



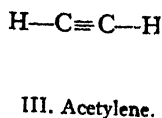
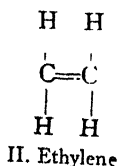
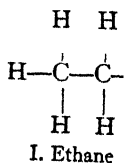
In a few compounds such as carbon monoxide, $\text{C}=\text{O}$, fulminic acid, $\text{HO}-\text{N}=\text{C}$ and others, carbon plays the part of a divalent element. It may also exist in the trivalent state in triphenylmethyl, and other compounds.

2. *The four valencies of carbon are equivalent to one another*, since the replacement of any one of the four hydrogen atoms in methane by the same monovalent atom, or group of atoms, always yields the same monosubstitution product.

The equivalence of the four carbon valencies is established by the fact that compounds such as CCl_4 possess zero dipole moment (see p. 70).

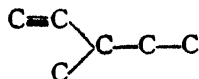
3. *Carbon atoms have a great capacity for combining with one another*. Recognition of this fact was of the greatest importance for the development of structural chemistry, since it led directly to the possibility of writing constitutional formulæ for carbon compounds. In the union of carbon atoms it is supposed that each atom is bound by a valency, or several valencies, to a neighbouring atom; the remaining valencies can then be saturated by hydrogen, or other simple or complex groups. Two carbon atoms may thus be linked together with one, two, or three valencies, these being termed single, double, or triple bonds respectively, e.g. $\text{C}-\text{C}$, $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$.

Those substances in which, as in I, only singly bound carbon atoms occur, are called saturated carbon compounds, whereas those, as in II and III, containing double or triple bonds are known as unsaturated.

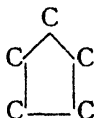
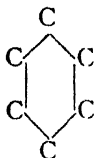


¹ It should be borne in mind that oxygen in organic compounds may under special conditions be tetravalent (see Collie and Tickle, *J.*, 1899, 75, 710; and Baeyer and Villiger, *Ber.*, 1901, 34, 2685) and carbon possibly trivalent.

In a similar way it is possible for three, four, or any larger number of carbon atoms to combine together. The final product may be an open chain such as

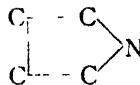
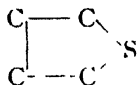
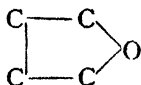


or closed chains or rings of the type



A number of important open chain carbon compounds are found in animal and vegetable fats. Consequently that section of organic chemistry which treats of open chain compounds is known as the fatty series, and a substance belonging to this class as a *fatty* or *aliphatic compound*.

On the other hand, those containing closed chains come under the heading of *cyclic compounds*. If the rings consist entirely of carbon atoms, as in the above examples, they are termed *carbocyclic*; if in addition to carbon we have elements such as oxygen, sulphur or nitrogen, taking part in the formation of rings of the type

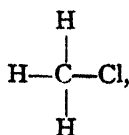


the compounds are termed *heterocyclic*.

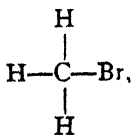
Among the carbocyclic rings, the one containing six carbon atoms with six free valencies possesses a special interest. From it are derived substances classed as *aromatic compounds* or *benzene derivatives*.

(b) Substitution, Radicals, Isomerism

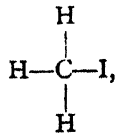
Under suitable conditions the elements in organic compounds may be replaced, or substituted, in equivalent proportions by other elements. Once again considering the simplest compound of carbon, methane, it is possible for one of its hydrogen atoms to be replaced by one atom of chlorine, bromine or iodine, or by a group of atoms, such as .OH, having one free bond :—



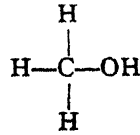
Methyl chloride



Methyl bromide



Methyl iodide



Methyl alcohol.

Such groups of atoms, which still exhibit free affinity and therefore

are not stable in the free state, are often transferable as such from one compound to another, and are termed **radicals** or **groups**. The group OH is known as hydroxyl, and since it possesses only one free affinity is monovalent. By the removal of successive atoms of hydrogen from methane we may derive the following :



Methyl



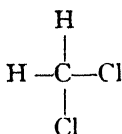
Methylene



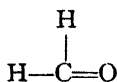
Methenyl or methine.

which are mono-, di- and trivalent radicals respectively.

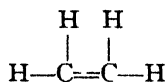
In the same way it is easy to understand that two atoms of hydrogen may be replaced either by two monovalent atoms or groups, or by one divalent atom or group, as illustrated in the following examples :



Methylene chloride

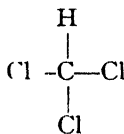


Formaldehyde

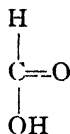


Ethylene.

Similarly three hydrogen atoms of methane may be substituted by three monovalent atoms or radicals, by one monovalent and one divalent atom (or radical), or by a trivalent atom (or radical), as in the following compounds :



Chloroform

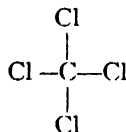


Formic acid

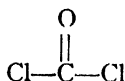


Acetylene.

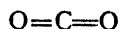
Finally, all four hydrogen atoms may be replaced by four monovalent atoms or radicals, etc., as in—



Carbon tetrachloride



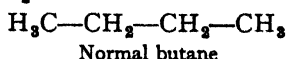
Phosgene



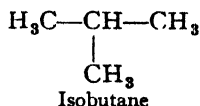
Carbon dioxide.

The substitution of hydrogen in methane by the radical CH_3 will be considered in more detail. When an atom of hydrogen in CH_4 is exchanged for the monovalent radical CH_3 , the hydrocarbon ethane, $\text{H}_3\text{C}-\text{CH}_3$, is produced. If in this compound H is again replaced by CH_3 , we obtain $\text{CH}_3-\text{CH}_2-\text{CH}_3$, propane. Obviously there is only one ethane or propane possible, since it is immaterial which hydrogen atom in methane or ethane is substituted. If, however, a hydrogen atom in propane is once again exchanged for CH_3 , two isomeric compounds may be formed, according to whether the H replaced is situated in one of the two

CH_3 groups or in the CH_2 . In the first case normal butane is obtained



and in the second isobutane,

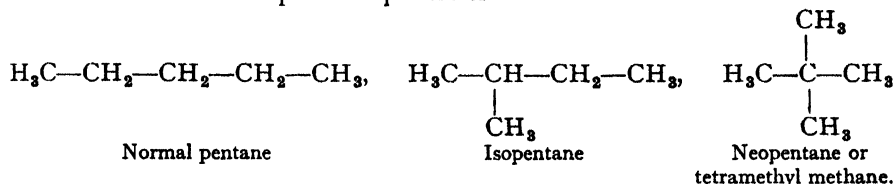


both of the composition C_4H_{10} .

As in numerous other cases, the cause of isomerism in the butanes is the different constitution of the carbon chains. Normal butane contains a straight carbon chain, whereas isobutane has a branched chain.

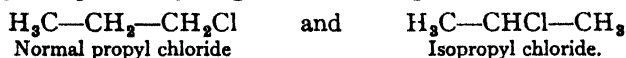
Isomerism of this type involving a different structure, or manner of linking, of the carbon chain or nucleus is termed **chain** or **nuclear isomerism**.

It is seen from the foregoing that there are two ways of linking up four carbon atoms; and if in a similar manner we derive from the formulæ of the two butanes the corresponding compounds with five carbon atoms, we find there are three possible pentanes—



With an increasing number of carbon atoms, the number of different modes of linking, and therefore the possible number of isomers, increases with extraordinary rapidity. There are five hexanes, C_6H_{14} , nine heptanes, C_7H_{16} , and eighteen octanes, C_8H_{18} , theoretically possible.

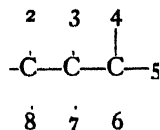
It is also possible for hydrogen atoms in all these hydrocarbons to be replaced by other elements or radicals. This gives rise to a different kind of isomerism from that discussed above. For example, different chlorine compounds may be derived from propane, $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_3$, according as the halogen replaces hydrogen in the CH_2 or one of the CH_3 groups—



The reason for the difference between these two compounds is no longer to be found in the different structure of their carbon chains, but in the different position of the chlorine atom in the same carbon chain.

Isomerism caused by the different position of substituents in the same carbon chain is termed **position isomerism**.

This can lead to conditions of great complexity, particularly when the carbon framework is saturated with different monovalent atoms or groups. It is thus theoretically possible to form over one hundred different derivatives of propane, C_3H_8 , if in the annexed formula the numbers 1 to 8 represent different monovalent atoms.



(c) Homologues

If we compare the formulæ of the simple hydrocarbons derived from methane by substitution, as described in the previous section,

CH_4
Methane

C_2H_6
Ethane

C_3H_8
Propane

C_4H_{10}
Butane,

we observe at once that each member of the series differs in its composition by CH_2 from the following member. Indicating the number of carbon atoms in these hydrocarbons by n , where n may be any whole number from 1 upwards, the number of hydrogen atoms is given by $2n+2$, and the series possesses the common formula $\text{C}_n\text{H}_{2n+2}$.

In all these hydrocarbons we may replace the hydrogen atoms by other atoms or radicals. On substituting a hydrogen atom in the above four hydrocarbons by a hydroxyl group, we obtain, irrespective of possible isomerides, the following compounds :

CH_3OH
Methyl alcohol

$\text{C}_2\text{H}_5\text{OH}$
Ethyl alcohol

$\text{C}_3\text{H}_7\text{OH}$
Propyl alcohol

$\text{C}_4\text{H}_9\text{OH}$
Butyl alcohol.

In this series also, each member differs from the next by CH_2 , and all are expressed by the general formula $\text{C}_n\text{H}_{2n+1}\cdot\text{OH}$.

Substitution by the most varied elements or radicals always results in the formation of groups of bodies whose members differ from one to another by CH_2 .

A group of similarly constituted compounds of this type is termed a **homologous series**, and its individual members **homologues**. It is easily understood that compounds which differ merely in the replacement of H by CH_3 , and are otherwise of similar structure, possess for the most part the same chemical properties. Thus the hydrocarbons CH_4 , C_2H_6 , C_3H_8 , C_4H_{10} , show great similarity in chemical behaviour, and the same is true of the hydroxyl compounds, CH_3OH , $\text{C}_2\text{H}_5\text{OH}$, $\text{C}_3\text{H}_7\text{OH}$, $\text{C}_4\text{H}_9\text{OH}$. Many other such series are met with in organic chemistry, and in consequence the study of the subject is very much lightened.

Kopp showed that in a homologous series the physical properties of the compounds change gradually from member to member (p. 66).

(d) Constitution of Unsaturated Carbon Compounds

Many instances of unsaturated compounds are known in organic chemistry, and these have for long been a fruitful subject of investigation. Earlier work in this direction led to the assumption of double and triple bonds, as illustrated in the formulæ—

$\text{H}_2\text{C}=\text{CH}_2$
Ethylene

$\text{HC}\equiv\text{CH}$
Acetylene.

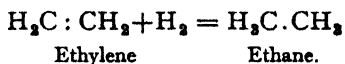
A number of unsaturated carbon compounds is also known in which the presence of a divalent carbon atom is assumed, as in

C : O	C : S	C : NH	C : NOH
Carbon monoxide	Carbon monosulphide	Hydrogen cyanide	Fulminic acid.

Nevertheless it should be noted that this hypothesis of multiple bonds is not indispensable for the explanation of unsaturated compounds, although it is still accepted by the great majority of chemists despite the objections that have been brought against it.

The theory of the existence of double and multiple bonds arose from the observation that all those reactions which would be expected to yield methylene, CH_2 , invariably lead to the formation of its homologue, ethylene, C_2H_4 . It was therefore assumed that free valencies could not exist on the carbon atom, and consequently of the two formulæ proposed for ethylene, $\text{H}_2\text{C}=\text{CH}_2$ and $\text{H}_3\text{C}-\text{CH}=\text{}$, Erlenmeyer decided in favour of the first.

The most characteristic property of unsaturated compounds is their ability to add on elements or radicals and pass into saturated compounds, for example—



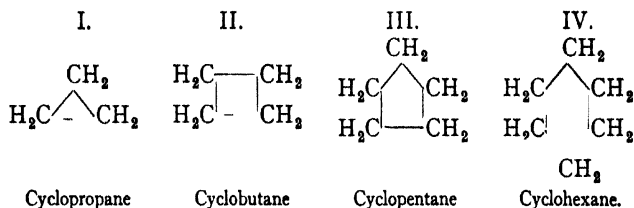
Doubly bound carbon atoms appear therefore to be less firmly united than singly bound atoms, whereas the reverse might have been expected. Baeyer attempted to explain this peculiarity by his strain theory.¹

From stereochemical considerations Baeyer came to the conclusion that the angle between the valencies of the carbon atom, according to the tetrahedral model (see p. 27), remains unaltered when two carbon atoms are united by a single bond ; but before a double bond can come into being, the respective valencies must be displaced from their original direction by a certain angle. A definite strain is thus set up in the molecule, rendering the multiple bond easily ruptured by suitable reagents to form a compound with single bonds and normally directed valencies. A similar, but even greater strain may be imagined to exist in compounds containing triple bonds. As was pointed out by Baeyer, the internal strain in the case of the polyacetylenes tends to manifest itself in the development of explosive properties.

In the same manner the distortion of the carbon bonds may be calculated for various cyclic compounds. It is found that this is comparatively large in cyclopropane (I), becomes less in cyclobutane (II) and disappears almost entirely in cyclopentane (III). In cyclohexane (IV) the displacement from the normal is somewhat greater than in the 5-membered compound. In qualitative agreement with Baeyer's strain theory it is found that the stability of the ring structure towards reagents increases

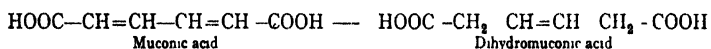
¹ See p. 381 for a fuller discussion.

as we pass from cyclopropane to cyclopentane, which is the most stable of the lower members of the series (see also p. 381 *et seq.*).



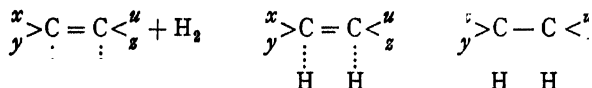
Later a detailed study of unsaturated compounds led to the conclusion that the double bond did not completely utilise the affinity between the two carbon atoms, but left a surplus on each atom which was termed *residual affinity*. These ideas, as developed by Thiele, aroused great interest and discussion.

Thiele's theory of unsaturated compounds was originally put forward in an attempt to explain the observation of Baeyer and Rupe, that when muconic acid is reduced the first step is the addition of two hydrogen atoms to the extreme ends of the hydrocarbon chain, with the formation of a new double bond in the centre. On further reduction this double

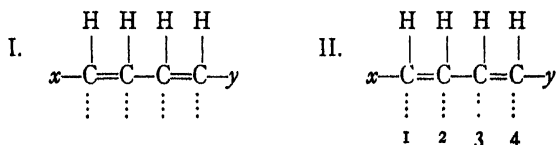


bond is also attacked. Many other conjugated dienes react similarly when reduced.

Thiele assumed that all such unsaturated compounds contain one or more double bonds, but that the two affinities of a double bond do not completely saturate one another, leaving a certain residual affinity or *partial valency* in excess on each carbon atom. This is illustrated graphically in the following formula, where the dotted lines indicate partial valencies. Addition to this compound follows by each new atom first attaching itself to a partial valency, subsequently taking up the full valency with the simultaneous disappearance of the double bond.



It is supposed that in a system of alternating single and double bonds such as I,



which Thiele described as **conjugated double bonds**, the two central partial valencies mutually saturate one another, so that addition first occurs at the ends of the system, in the 1, 4 positions (II).

Thiele illustrated the use of his hypothesis by a large number of examples, and it appeared at first to give a satisfactory explanation of the behaviour of many unsaturated organic compounds. In recent years, however, facts have come to light which are not in agreement with the rule of 1 : 4-addition. Thorpe and his co-workers¹ re-examined the behaviour of butadiene towards bromine and confirmed the simultaneous formation of two primary dibromo-addition products, one of which is 1 : 2- and the other a 1 : 4-compound, the former being usually in excess. Either of these compounds, on being heated, undergoes rearrangement to give a mixture of the two isomerides containing about 80 per cent. of the 1 : 4-compound, although the isomeric change is very slow at room temperature. Hence the process of addition to such a system is not as simple as is represented in Thiele's theory.



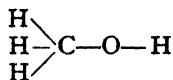
An investigation² of the addition of HBr to butadiene at -80° in the presence of antioxidants (*e.g.* diphenylamine, hydroquinone) shows that about 80-90 per cent. of the 1 : 2-addition product, $\text{CH}_2 : \text{CH} . \text{CHBr} . \text{CH}_3$, is formed together with 10-20 per cent. of crotyl bromide, $\text{CH}_3 . \text{CH} : \text{CH} . \text{CH}_2 \text{Br}$, resulting from 1 : 4-addition. At higher temperatures, however, isomerisation into crotyl bromide occurs, and this is the compound usually isolated.

In a similar manner isoprene, $\text{CH}_2 : \text{C}(\text{CH}_3) . \text{CH} : \text{CH}_2$, adds on hydrogen in the presence of platinum black to give in the first instance a mixture of 1 : 2, 1 : 4 and 3 : 4 derivatives,³ these three reactions proceeding simultaneously. The unsaturated cyclic compounds 1 : 3-cyclohexadiene and 1 : 3-cyclopentadiene also yield considerable proportions of 1 : 2-dibromo-addition products.⁴

(e) Derivation of Structural or Constitutional Formulæ

The constitutional or structural formula is derived from the molecular formula by building up every possible combination of the constituent atoms, consistent with the foregoing considerations of valency, and selecting that particular one which agrees best with the properties of the compound.

It is a comparatively simple matter to assign a formula where the number of atoms in the molecule is small. Thus a compound of molecular formula CH_4O must possess the structure given below, if we assume the valencies of C, O and H to be four, two and one respectively. In other cases it may be necessary to make a choice from several alternatives.

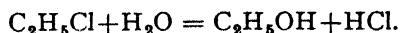


¹ E. H. Farmer, C. D. Lawrence and J. F. Thorpe, *J.*, 1928, 729; see also Straus, *Ber.*, 1909, 42, 2872. ² M. S. Kharasch, E. T. Margolis and F. R. Mayo, *J. Org. Ch.*, 1937, 1, 192; R. Voigt *J. pr. Ch.*, 1938, 151, 307. ³ S. V. Lebedev and A. O. Yakubchik, *J.*, 1928, 123. ⁴ Farmer and Scott, *J.*, 1929, 172.

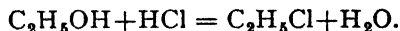
The final allocation of a structural formula should be made with reference to the following general considerations, based on laboratory experience :—

1. The possibility of converting the substance into, or of forming it from, compounds of known constitution. In this connection it may be noted that *when compounds undergo double decomposition, the new atom or radical entering into a molecule usually takes up the position occupied by the outgoing atom or radical.*¹ The structure of the radicals exchanged generally remains unaltered during this process.

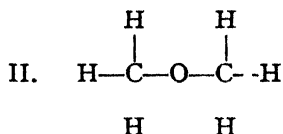
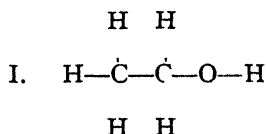
For example, ethyl chloride, C_2H_5Cl , for which there is only one possible constitution, is under certain conditions transformed into alcohol, C_2H_5O , by interaction with water :



Conversely, ethyl alcohol by treatment with hydrochloric acid regenerates ethyl chloride :

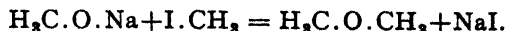


We must therefore assume alcohol to contain the radical C_2H_5- or $CH_3.CH_2-$, already known to exist in ethyl chloride, and consequently also the monovalent hydroxyl group $-OH$. For these reasons alcohol is allotted formula I below,

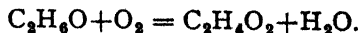


which is in complete harmony with its chemical behaviour. Of the six hydrogen atoms present, one obviously differs from the other five in its reactivity and the ease with which it is replaced by metals or radicals. Hence this hydrogen atom is assumed to be linked indirectly to carbon through oxygen.

Consideration of these facts leads to the rejection of the only other possible structure II for a substance of molecular formula C_2H_6O . The latter represents methyl ether, which is isomeric with ethyl alcohol. Here the six hydrogen atoms are all seen to be in the same state of combination. Formula II may also be derived from the formation of methyl ether by the interaction of sodium methoxide and methyl iodide :



As a further example, the constitution of acetic acid, $C_2H_4O_2$, may be examined. This substance is produced by the oxidation of ethyl alcohol, according to the equation



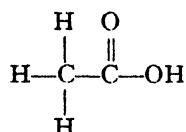
¹ In special cases, to be discussed later, a migration of atoms or radicals may occur

One of the four hydrogen atoms differs in its properties from the other three. It is readily replaced by metals or monovalent radicals and its whole behaviour shows it to be united to oxygen in the form of a hydroxyl group, and not directly attached to carbon.

The first step was therefore to write acetic acid as $C_2H_3O(OH)$, and next to determine the structure of the C_2H_3O radical. This problem was solved by Kekulé, who showed that the three hydrogens must be attached to one and the same carbon atom, since potassium acetate, when heated with potassium hydroxide, yields methane and potassium carbonate.



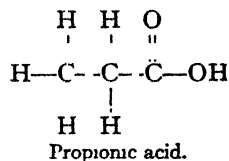
The constitution of acetic acid is therefore assumed to be



It will be seen when we come to deal with the properties of the acid that this formula is in good agreement with its chemical behaviour.

2. *The chemical and physical character of a compound is a function of its molecular structure*, and the chemical similarity of a number of compounds is dependent on the common presence of certain "typical" groups of atoms. Constitution is therefore frequently decided by comparing the physical or chemical properties of the substance with those of a compound of known structure. Every alcohol, for example, contains the hydroxyl group ($-\text{OH}$), and all compounds which show those properties characteristic of the alcohols may also be assumed to contain a hydroxyl group in the molecule.

The large majority of organic acids contain the carboxyl group, $-\text{COOH}$, as given above under acetic acid. If then primary propyl alcohol, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH}$, yields on oxidation an acid of the molecular formula $C_3H_6O_2$, the latter probably contains the group $-\text{COOH}$ and possesses the structural formula given above.



Intramolecular Rearrangement

As already indicated, the atom or radical entering a molecule by double decomposition occasionally fails to occupy the position of the out-going atom or radical, more particularly if the reaction takes place at a high temperature.

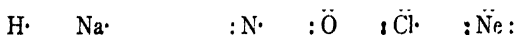
Hence some uncertainty attaches to a constitutional formula deduced by any single one of the methods described under I. The result can only be regarded as probable when derived from the consideration of several different reactions, each of which leads to the same conclusion.

In general, a structural formula is only accepted as established beyond doubt when it has been confirmed by synthesis.

The Electronic Theory of Valency¹

Great advances have been made in our conception of valency by interpreting it in the light of the electronic theory, according to which atoms are built up solely of *protons* and *electrons*. A *proton* is a unit of positive electricity having extremely small dimensions and a mass of 1.007 ($O = 16$). An *electron*, or unit of negative electricity, is of considerably greater dimensions than a proton but only about $1/1840$ of its mass. Atoms, then, being externally neutral bodies, are composed of equal numbers of protons and electrons. All of the protons, with about half of the electrons, are packed closely together into a small space constituting the atomic *nucleus*. The remainder of the electrons, the number of which gives the *atomic number* of the atom, are in rapid rotation in orbits around the nucleus and hence occupy a much greater volume than the latter. These planetary electrons arrange themselves in layers round the nucleus, each layer containing a definite number corresponding to the condition of maximum electrical stability. The chemist, however, is concerned almost exclusively with the outermost layer, since the chemical properties of the atom, including that of valency, depend almost entirely on the number and disposition of the electrons in the *outer shell* which is therefore termed the *valency shell*.

Except for the transition elements in group 8 and the rare gases in group 0, the number of electrons in the valency shell corresponds to the number of the group into which the element falls in the periodic scheme. Thus hydrogen and the alkali metals, Na, K, etc., in the first group have only one valency electron, carbon in the fourth group has four, nitrogen has five, oxygen six, and chlorine seven. In the rare gases from neon upwards, there is a complete outer group of eight electrons. These atoms can be represented diagrammatically as follows:—



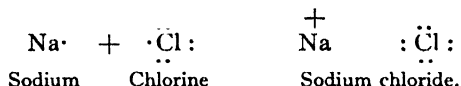
Chemical reactions are supposed to occur owing to the tendency of valency shells to assume a more stable arrangement. For the majority of the common elements stability is reached when there is an outer shell of eight electrons (an *octet*); for hydrogen and the rare gas helium however, the stable number is two. In the case of elements of groups I and II, possessing one and two valency electrons respectively, the stable condition may be attained by the complete loss of these electrons. This change occurs on ionization and results in the exposure of the underlying shell of electrons, which is already in its most stable arrangement

¹ For detailed treatment see Sidgwick, *The Electronic Theory of Valency* (Oxford University Press, 1927); H. B. Watson, *Modern Theories of Organic Chemistry* (Oxford University Press); G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry* (Prentice Hall, Inc, 1941); J. C. Speakman, *An Introduction to the Modern Theory of Valency* (Arnold 1949); G. I. Brown, *Modern Valency Theory* (Longmans, 1953).

lements of group VII, on the other hand, may readily complete their octets by gaining or even sharing an electron from another atom. In the rare gases the valency shell exists in a formation of maximum stability, hence these elements have no chemical reactivity whatever.

Actual combination between two atoms may be supposed to occur in one of two ways, both of which were suggested by Lewis.

1. Union may take place by an atom completely transferring one or more of its electrons to another atom. As atoms are externally neutral groups of protons and electrons, this leaves the first atom positively and the second negatively charged. Combination of this type is found chiefly among salts of acids and bases, and is known as **electrovalency**. The oppositely charged ions may be regarded as separate entities, normally held together by electrostatic attraction. The equation given below illustrates the electronic changes which take place when sodium and chlorine combine to give sodium chloride. In order to make these and the following formulæ clearer, the electrons belonging to different atoms are in some cases indicated by different signs.

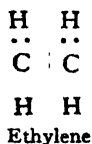


2. A type of valency which is of much more frequent occurrence in organic compounds is that of **covalency**. In this case the two atoms unite by holding a pair of electrons in common, one being contributed by each atom. For example, the oxygen atom in water has increased its sextet to an octet by acquiring a share in two other valency electrons from the atoms to which it is linked. At the same time each hydrogen atom has attained a stable shell of two by sharing an oxygen electron. In methyl alcohol the four electrons in the outer shell of the carbon atom are raised to eight by sharing with three hydrogen electrons and one oxygen electron. Each pair of shared electrons constitutes a non-ionizing



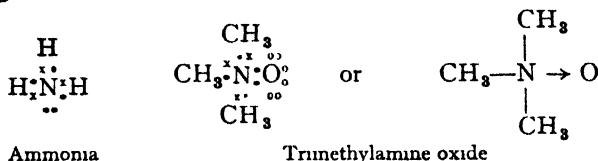
and as commonly pictured in organic formulæ. For simplicity of representation the electrons are figured as static; but it must be remembered that they are in reality supposed to be in a state of rapid motion.

The ordinary *double bond*, as in $\text{C}=\text{C}$ or $\text{C}=\text{O}$, is regarded as a double co-valency, *i.e.* as four electrons shared between two atoms, two electrons being supplied by each. A double bond of this type is symmetrical in structure, and has a plane of symmetry containing the double linking.



3. Another form of co-valency, the development of which is chiefly due to Lowry and to Sidgwick, is that in which *one* of the atoms supplies *both* of the electrons required for the union. This mode of union was first applied to certain inorganic compounds by Lewis.

In order that combination of this kind may be possible, one of the atoms (the *donor*) must have at least two valency electrons (termed a *lone pair*) which are not concerned in union with any other part of the molecule, and the other atom (the *acceptor*) must be able to take up two electrons to form a more stable arrangement.¹ Many atoms, even when in the combined state, possess one or more of these lone pairs of electrons. Oxygen in water has two and nitrogen in ammonia or organic bases has one. Under suitable conditions, therefore, O and N in these compounds may function as *donor atoms*. Atomic oxygen, on the other hand, has a valency shell of six electrons (two less than the stable arrangement) and may play the part of an *acceptor atom*. Thus in trimethylamine oxide, $(\text{CH}_3)_3\text{NO}$, the two nitrogen electrons which were unattached in trimethylamine are supposed to be shared with the oxygen. Sidgwick represents this kind of linking by a short arrow, *e.g.* $\text{N} \rightarrow \text{O}$. The single line indicates that it is a link formed by the sharing of two electrons, and the direction of the arrow shows that both the electrons are provided by the nitrogen atom.



An arrangement such as this necessarily implies that the molecule has developed polarity. The nitrogen atom becomes positively charged owing to two of its electrons being less in its proximity than previous to the union, and the oxygen atom becomes negatively charged, having two additional electrons in its outer shell. Lowry, who first proposed the above electronic formula for the amine oxides, therefore described the linking between N and O as a **semi-polar double bond**, since it appears to possess the combined properties of a co-valence and an electrovalence. The term **co-ordinate link** (Sidgwick) is now generally applied to such bonds. It must be emphasised, however, that later investigations of the physical properties of such compounds do not support the earlier assumption that the charge on the oxygen atom is equivalent to the complete transfer of an electron from nitrogen to oxygen.²

Experimental verification of the presence of co-ordinate links is given by bond length measurements. For example, in trimethylamine oxide the length of the N—O linkage is 1.36 ± 0.03 Å in agreement with the value calculated from atomic radii for a single bond link and in contrast

¹ Sidgwick, *The Electronic Theory of Valency*, p. 116. ² Compare R. F. Hunter and R. Samuel, *Chem. and Ind.*, 1935, 54, 31, 635.

QUANTUM THEORY

o the value 1.15 Å for the N = O bond. The bond length is clearly the same as would be expected for a single covalent bond.

It has been suggested that in order to preserve the octet a nitro group should be formulated with one double bond and one of the semi-polar type. Measurements of dipole moments have shown, however, that the electronic states of the two oxygen atoms are identical. This is now explained on the theory of **resonance** or **mesomerism**. In its original form this assumed that the molecule oscillated rapidly between

the two states $\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{N} \rightarrow \text{O} \end{array} \quad \text{N} \rightarrow \begin{array}{c} \text{O} \\ \parallel \\ \text{O} \end{array} \right)$; it is now regarded as having an

intermediate structure which is not capable of being represented by our present symbols (see p. 77).¹

From the foregoing pages it will be seen that the usual formulæ of the organic chemist are readily translated into electronic formulæ by replacing each single non-ionizing bond by a pair of shared electrons; each ionizing bond by the transfer of an electron; and each double bond by four shared electrons, except in cases where a co-ordinate link or semi-polar double bond is known to be present.

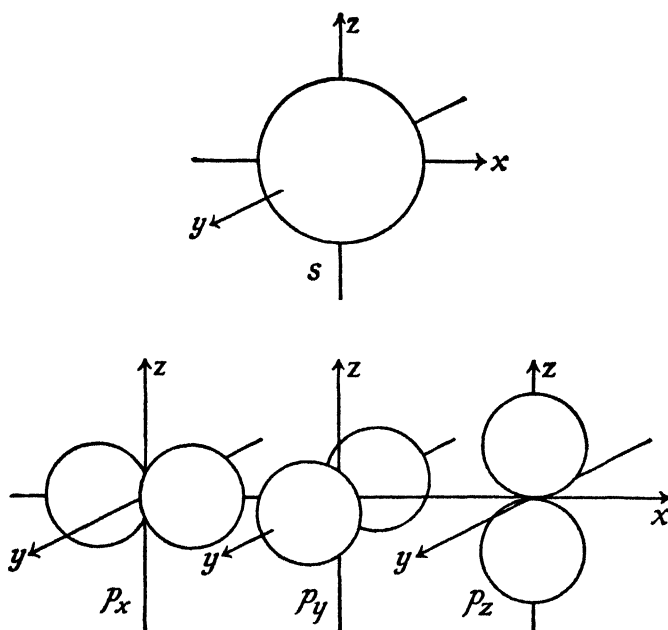
Quantum Theory of the Chemical Bond ²

In 1916 G. N. Lewis showed that valency is essentially an electronic phenomenon, and since then, as the result of the quantum mechanic treatment of spectrographic data, a satisfactory picture of atoms (including the carbon atom) in terms of electronic movement has been developed. This provides an explanation of such fundamentals as how atoms combine to form molecules, the quadrivalency of carbon, the tetrahedral arrangement of the carbon bonds in saturated compounds, and the double bond. The new theory thus gives an explanation of optical and geometrical isomerism, and, as we shall see, of the stable six-membered carbon ring characteristic of the aromatic compounds.

The first picture of the atom in terms of electronic behaviour was given by Niels Bohr in 1913. According to this, the extra-nuclear electrons move round the nucleus in well-defined orbits, each orbit being associated with a certain energy. Hence the term *energy levels* was frequently applied to these orbits. Bohr's theory led to great advances, but was shown eventually to be inadequate and has now been replaced by one based on quantum mechanics. This does not give rise to such a clear-cut picture as that of Bohr, but it can be visualised sufficiently accurately to be used by the organic chemist, though he may not fully understand the mathematical and physical processes upon which it is based.

¹ See Sidgwick, *Ann. Reports*, 1934, 37. ² For a more detailed account see C. A. Coulson, *Quarterly Reviews of the Chemical Society*, 1947, 1, 144. *Proc. Roy. Soc. Edinb.*, 1941, 62, 115. *Valency*, by W. G. Palmer (Cambridge University Press, 1945). C. A. Coulson, *Valence* (Oxford University Press, 1952).

Electrons are no longer regarded as moving in certain orbits, but are described as moving in regions or volumes known as *orbitals*. Orbitals may be of different types, of which two are of immediate concern to the organic chemist. These are illustrated in the accompanying diagram. In the hydrogen atom there is one electron moving round the nucleus and it moves in a spherical orbital known as a *s-orbital*. This is another way of stating that we cannot quite define the position of this electron in space at any given instant, but we can say that in all probability the electron will be found within this sphere. In the carbon atom there are six extra-nuclear electrons and some of these move in *s-orbitals*. Others, however, are to be found in *p-orbitals* or "dumb-bell orbitals." These differ not only in shape from the *s-orbitals* but also in having *directional*



properties. This is shown in the diagram, which represents three *p-orbitals*, p_x , p_y , p_z , according to their axial orientation.

An important property of electrons is their *spin*. A simple description of this term cannot be given here, but it is sufficient to say that any two electrons may have either the same or opposite spins. According to an important principle, the *Pauli Exclusion Principle*, no atom or molecule may have more than two electrons in one orbital and these two electrons must have opposite spins.

To understand the electronic behaviour of carbon it is helpful to consider first some of the other simple elements.

As we have seen in the hydrogen atom there is one K-shell electron moving in an *s-orbital*. It is described as a $1s$ electron, the numeral showing it to be a K-shell electron and the letter denoting the type of

orbital. Helium is represented by $1s^2$ signifying that it has two K electrons moving in an s -orbital. Lithium has in addition to these two electrons an L-shell electron to which is assigned an s -orbital. Its electronic configuration is therefore denoted by $1s^2 2s$. Building up in this way we obtain for the carbon atom in the normal state the arrangement $1s^2 2s^2 p^2$ or more fully $1s^2 2s^2 p_x p_y$. This means that in addition to the two pairs of s -electrons (*i.e.* electrons which move in s -orbitals) there are two unpaired p electrons.

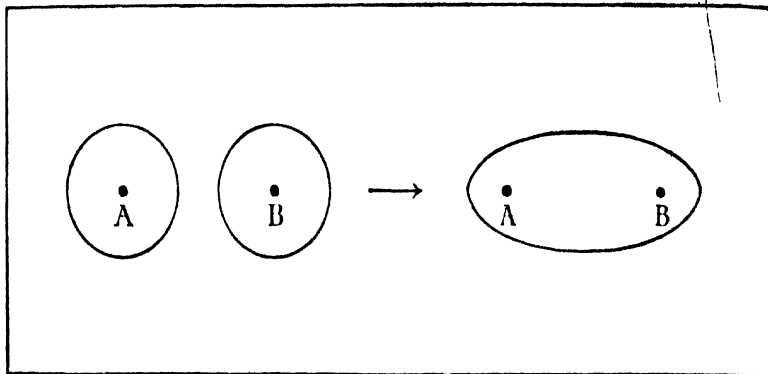
Orbital . . .	$1s^2$	$2s^2$	$2p$	$2p$	$1s^2$	$[2s p^3]$			
Spin . . .	$\uparrow \downarrow$	$\uparrow \downarrow$	\uparrow	\uparrow	$\uparrow \downarrow$	\uparrow	\uparrow	\uparrow	\uparrow
No. of electrons	2	2	1	1	2	1	1	1	1
	Normal state				Valency or excited state				

Electronic Configuration of the Carbon Atom

Now it is known that the valency of an element is given by the number of *unpaired* electrons in the atom. Thus hydrogen has a valency of 1, helium a valency of 0, lithium 1, and so on. The $1s^2 2s^2 p^2$ arrangement of carbon is obviously unsatisfactory, since it implies a valency of two, a value quite out of harmony with the firmly established quadrivalency of carbon. One way out of the difficulty is to uncouple the $2s^2$ electrons giving then four unpaired electrons, $1s^2 2s p_x p_y p_z$. This would still be unsatisfactory, implying as it does the formation in compounds such as CH_4 of three bonds identical with each other but differing from the fourth—a result at variance with a mass of experimental data. Pauling overcame this objection by *hybridising* the orbitals, and by a mathematical process found that *two* stable electronic configurations are possible. The first is applied to the problem under consideration, and the second to the nature of the double bond (p. 24) and of the benzene ring (p. 432). Pauling showed that for the formation of compounds such as methane carbon must have four identical electrons (hybridised $2sp^3$), and in addition the carbon bonds are at an angle of $109^\circ 28'$ to one another and are directed towards the corners of a regular tetrahedron. The atom is thus ready for the formation of saturated molecules with the van't Hoff configuration.

The formation of saturated molecules may be regarded simply as the formation of the requisite bonds between the atoms concerned. For example, methane is formed by the interaction of a carbon atom and four hydrogen atoms, and the fundamental Lewis picture that each bond results from interaction of an electron from the carbon atom and one from a hydrogen atom still obtains. The new theory, however, gives a more complete picture of this electronic interaction. In the molecule the bonding electrons no longer move in atomic orbitals but in *molecular orbitals*. This means they are no longer monocentric but bicentric. In

the simplest example, the combination of two hydrogen atoms to form a hydrogen molecule is represented in the figure. The two atomic orbitals of the separate hydrogen atoms combine to form one molecular orbital in which both electrons are pictured as moving round both the atomic nuclei. This type of orbital is known as a σ -type orbital, or more picturesquely as a "sausage-type." It is in this region that the bonding electrons (with opposite spins) are to be found. This is another way of stating that the bonding electrons are to be found between the two nuclei and provides formal justification of the Lewis picture of the bond.

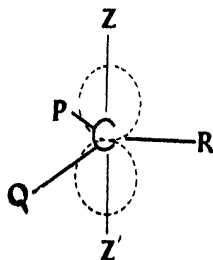


It appears that the most stable molecule results when the constituent atomic orbitals overlap to the maximum extent possible. This *principle of maximum overlapping* provides a theoretical basis for the known facts of stereochemistry. For when the four unpaired electrons of carbon in the hybridised tetrahedral orbits discussed above form four identical bonds with (say) hydrogen, the resulting tetrahedral configuration permits the maximum overlapping of the carbon and hydrogen orbitals.

The Double Bond

The double bond was formerly visualised as composed of two single bonds or four electrons. The quantum theory has given rise to a somewhat different picture, though the bond still consists of four electrons.

It has been shown above that single or σ -bonds consist of "sausage-type" orbitals formed from a hybridised $2sp^3$ electron configuration of the carbon atom. There is, however, another way in which hybridisation may yield a stable configuration. In this type—the *trigonal type*—one $2s$ and two $2p$ orbitals are hybridised to three identical orbitals all lying in one plane at an angle of 120° to one another as in the diagram. For simplicity the three orbitals are represented by the heavy lines P, Q, and R. The remaining orbital, a $2p$ or π -orbital, is situated at right angles to the other orbitals (along ZZ' in the diagram).



A little consideration is sufficient to show that this trigonal configuration leads readily to the formation of a double bond. It is known from electron diffraction measurements that the simplest double-bonded compound, ethylene, $\text{CH}_2:\text{CH}_2$, has a planar molecule with bond angles of approximately 120° .



Obviously such a double bond is most easily formed from two carbon atoms of the trigonal type. Two of the planar orbitals of each carbon atom overlap the orbitals of two hydrogen atoms and the third takes part in forming a σ -bond between the carbon atoms. This leaves the two π -electrons and these complete the formation of the double bond by overlapping as much as possible. The maximum overlapping, *i.e.* the formation of the most stable bond, occurs when the π -orbitals are parallel to one another. This results in a planar molecule and also accounts for the "clamping" or lack of free rotation of olefinic molecules.

Summarising we may say that a double bond is not simply a combination of two similar single bonds, but is composed of two linkages—a π -bond superposed on a σ -bond. Expressed differently: a double bond is composed of four electrons, two moving in σ -type orbitals and the other two in π -type orbitals.

π -Orbitals cannot overlap to the extent observed with σ -orbitals. In consequence the π -electrons are more easily loosened and the well-known reactivity of the double bond is due to this fact.

A further example of trigonal hybridisation is discussed later when the constitution of benzene is considered (p. 432).

II.—STEREOCHEMISTRY ¹

Whereas the theory of structure treats only of the sequence and manner in which the atoms are linked together within the molecule, stereochemistry concerns itself with those chemical phenomena which are directly attributable to the *configuration*, or disposition of the atoms in space. That type of isomerism which involves substances of the same constitution, but different configuration, is called **stereoisomerism**, and the substances are known as *stereoisomerides*.

From the historical point of view stereochemistry has developed logically from the theory of structure. At first it was found possible to explain the number and properties of almost all compounds of similar

¹ See K. Freudenberg, *Stereochemie* (1933); T. M. Lowry, *Optical Rotatory Power* (1935); G. Wittig, *Stereochemie* (1930); Werner, *Lehrbuch der Stereochemie*, Jena, 1904; P. Walden, *Fünfzig Jahre Stereochemischer Lehre und Forschung*, Ber., 1925, 58, 237.

molecular formula by assuming a difference of constitution. One by one, however, cases of isomerism were discovered which could not be explained on the ground of structural dissimilarity, and these were for a time classed as "physically isomeric substances," without any reason being assigned for the isomerism.

Stimulated by the work of Pasteur and Wislicenus, a stereochemical theory of the isomerism of optically active compounds was developed independently and almost simultaneously in 1874 by van't Hoff and Le Bel. Since then many investigators have made valuable contributions to this subject and none more so than Emil Fischer in his brilliant researches on the sugars.

The stereochemistry of nitrogen has similarly been advanced by the work of Hantzsch and Werner, Le Bel, Pope and Peachey, Wedekind, Mills and others.

1. Stereochemistry of Carbon

According to their behaviour the stereoisomeric carbon compounds may be divided into two groups as follows :—

A. Substances which are identical in all their chief properties, but differ in their "optical activity" or action on polarised light, when examined in the fused state or in solution. Such compounds are termed **optical isomerides**, **optical antipodes** or **enantiomorphs**, and with few exceptions contain within the molecule at least one *asymmetric carbon atom* (*cf. footnote, p. 29*). By this term is understood a carbon atom whose four valencies are united to four *different* monovalent atoms or groups.

B. Substances which, having the same structural formula, differ in all their physical and many of their chemical properties, but exert no influence on polarised light. These are compounds containing double bonds and are generally described shortly as **geometrical isomerides**. Many of the saturated cyclic compounds also exhibit this kind of isomerism. (See cycloparaffin series, p. 380.)

In their original publications van't Hoff and Le Bel showed that both of these types of isomerism could be explained on the assumption that the valency bonds were arranged in three dimensions around the carbon atom.

A. OPTICAL ISOMERISM¹

According to van't Hoff's fundamental hypothesis of stereochemistry, the four valency bonds of the carbon atom are imagined to be directed towards the summits of a regular tetrahedron, at the centre of which

¹ See *Optical Activity; its Study, Terminology and Uses*. M. P. Balfe, *Science Progress*, 1950 151, 459.

lies the atom itself. It is easily seen by reference to figures 1 and 2¹ that a substance of the type $Cabc d$, in which a , b , c and d are four

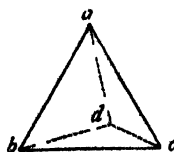


FIG 1.

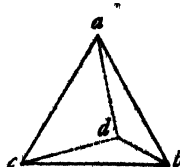


FIG 2.

different atoms or groups, can assume two different configurations which are not superimposable. A carbon atom such as this is described as asymmetric.

One configuration is a non-superposable mirror-image of the other, and the difference between them is comparable with that existing between the right hand and the left. This *enantiomorphism* or mirror-image relationship of the molecules is repeated in the optical and crystallographic properties of the substances; but in most remaining physical and chemical properties the compounds are identical. Structural figures such as 1 and 2, expressing the spatial arrangement of the atoms, are called space formulæ, and illustrate the fact that *the molecule of an optically active compound possesses no plane of symmetry*.

In studying stereochemical problems it is advisable not only to visualise the space formulæ indirectly on the plane of the paper, but also directly by use of space models as devised by Kekulé, van't Hoff and others. The simplest type of model is that in which the four valency bonds are represented by four pieces of rubber tubing, connected together at one end, and directed towards the corners of a regular tetrahedron. Coloured balls attached to the tubes by rods represent the different groups.

Van't Hoff's theory of the carbon atom is supported by Bragg's X-ray analysis of the structure of the diamond,² in which the carbon atoms are found to be united by tetrahedrally directed valency bonds.

In its main essentials Le Bel's theory agrees with that of van't Hoff. Le Bel, however, made no assumption regarding the geometrical arrangement of the valency bonds in space. He stated that molecular asymmetry will necessarily exist if the four different radicals are arranged in space around the carbon atom, whatever may be the geometrical form of the molecule. In this respect van't Hoff's ideas accord more closely with later developments of stereochemistry.

Certain inorganic substances (*e.g.* sodium chlorate) are optically active in the crystalline state. This is due to the *molecules* being arranged in an asymmetric manner within the crystal and the activity therefore disappears when the crystal passes into solution. The optical activity of carbon and other compounds in solution is a consequence of the asymmetric arrangement of the *atoms* in the molecule. In some cases the crystals of such compounds also possess optical activity.

¹ For the sake of clearness the carbon atom, which is supposed to lie at the centre of the tetrahedron with its bonds directed towards a , b , c and d , is omitted in the space formulae. The letters a , b , c , d represent the four different atoms or radicals attached to the asymmetric atom.

² W. H. Bragg, *Proc. Roy. Soc.*, 1913, 89 A, 277.

Compounds containing one Asymmetric Carbon Atom

The most striking difference between isomers containing an asymmetric carbon atom lies in their optical activity in the liquid or dissolved state. To every active compound rotating the plane of polarisation through a certain angle in a given direction, there corresponds an isomeride which, otherwise identical in properties, rotates the plane of polarised light to the same extent in the opposite direction. The two enantiomorphs differ only in sign of rotation, and are therefore termed *optical antipodes*. They are distinguished arbitrarily as dextrorotatory and laevorotatory modifications, or more commonly by prefixing the letters *d*- and *l*- (or + and -) to the name of the substance, *e.g.* *d*- and *l*-lactic acids. Their configuration is denoted by the letters D and L (see p. 237).

If equimolecular quantities of the (+) and (-) forms of a compound are mixed with one another, a product is obtained in which all optical activity disappears, owing to the mutual or *external compensation* of the two constituents. Inactive products of this type are called *racemic compounds* or *mixtures*¹ and are usually distinguished by the prefix *r*- or *dl*-. When crystalline they are frequently definite compounds having double the molecular weight of the (+) or (-) forms. In the fluid state or in solution racemic compounds exist as a mixture of the *r*- form in equilibrium with equivalent amounts of the (+) and (-) modifications, thus recalling the behaviour of double salts.² By methods to be described later it is possible to resolve these racemic compounds into their active components.

A few rare cases have been observed, notably in the camphor series, in which no definite compound is produced, but the two optical enantiomorphs form mixed crystals with one another, the product being termed a *pseudoracemic mixture*.³

A typical instance of a compound containing an asymmetric carbon atom is lactic acid, $\text{H}_3\text{C} \cdot \text{CH}(\text{OH}) \cdot \text{COOH}$, which occurs in two optically

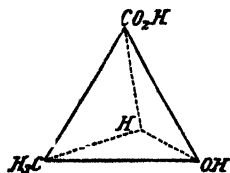


FIG. 3.

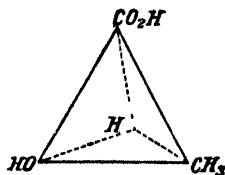


FIG. 4.

active modifications and an optically inactive or racemic form. The two optical antipodes are related to one another in the manner shown in Figs. 3 and 4. They thus have the same structure but different configurations.

¹ The name is derived from racemic acid, the first representative of this class to be observed.

² Racemic compounds are not necessarily *completely* dissociated into the *d*- and *l*- forms in solution. Cotton has shown that on mixing equimolecular solutions of copper *d*- and *l*-tartrates, dissolved in alkali, the colour at once deepens, thus indicating compound formation (*Ann. Chim. Phys.*, 1896, 8, 347; *Trans. Farad. Soc.*, 1930, 377). ³ See Pope and Read, *J.*, 1913, 103, 1515.

It can readily be demonstrated that the existence of these isomerides, like the property of optical activity itself, is dependent on molecular asymmetry. With the destruction of the asymmetry of the carbon atom—for example, when a molecule of the formula $C a b c d$ is converted into $C a b c_2$ —both optical activity and isomerism disappear.¹ Thus the reduction of either of the optically active malic acids, $HOOC \cdot CH_2 \cdot CH(OH) \cdot COOH$, leads to the formation of the same inactive succinic acid, $HOOC \cdot CH_2 \cdot CH_2 \cdot COOH$.

Compounds with two or more Asymmetric Carbon Atoms

As the number of asymmetric carbon atoms in a compound becomes greater, the number of possible isomerides increases rapidly. *In general, a compound of unsymmetrical structure containing n asymmetric carbon atoms can exist in 2^n optically active isomerides,*² made up of a number of pairs of mirror-image forms possessing equal and opposite rotations. This general statement postulates a structural dissimilarity between the asymmetric atoms involved; if this is not the case, and the molecule is symmetrically built, certain of the asymmetric atoms will be structurally alike and consequently some of the possibilities of isomerism will vanish.

It is only feasible at this stage to discuss the isomerism dependent on the presence of two asymmetric atoms within the molecule. Examples of greater complexity, such as those offered in the sugar series, will be examined later under their respective headings.

As already stated above, compounds containing two dissimilar asymmetric carbon atoms are capable of existing in 2^2 , or four, optical isomerides, made up of two pairs possessing equal and opposite rotatory powers; to these must be added the two (inactive) racemic forms. This can be deduced in a simple manner by distinguishing the two atoms by the letters A and B, and their different spatial configurations by the signs + and -. We have then the following active compounds:



An example of this type is cinnamic acid dibromide,

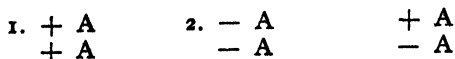


which is known to occur in four active as well as two racemic forms.

Compounds possessing two asymmetric but structurally similar carbon atoms, of the general formula $C_{abc}-C_{abc}$, exist in three different configurations, two of which are optically active antipodes; the other is represented by an internally compensated structure and cannot be resolved into active components (see p. 30). In addition, the two active enantiomorphs may unite to produce a racemic form.

¹ Those compounds which contain an asymmetric carbon atom form a special class in which the spatial arrangement of the atoms within the molecule is such that no plane of symmetry is present. Such compounds must occur in two modifications, the space formulæ of which are mirror-images of one another. As Pasteur first recognised, they are distinguished by enantiomorphous crystal structure and optical activity of contrary sign. ² Cf. however, p. 788.

The different modifications can be derived in a manner similar to that shown above, by placing $A = B$, in which case configurations 3 and 4 become identical.



The substance represented by 3 is optically inactive, despite the presence of two asymmetric complexes, owing to the activity of the one group being equal and opposite to that of the other. In other words, it is *internally compensated*. Compounds of this type are also described as *i*- or *meso*-forms. This inactive and non-resolvable form cannot occur in cases where there is only one asymmetric atom present in the molecule, and is to be distinguished carefully from the inactive, *externally compensated*, racemic type which by special methods can be resolved or separated into its optically active components.

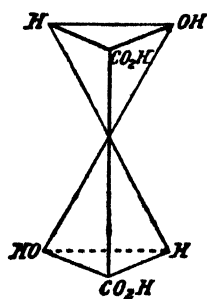


FIG. 5.

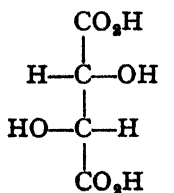
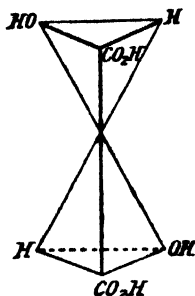
1. *d*-Tartaric acid

FIG. 6.

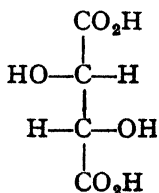
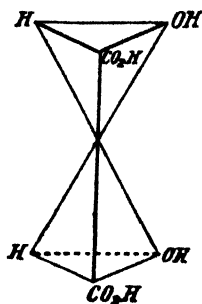
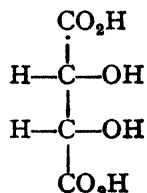
2. *l*-Tartaric acid

FIG. 7.

3. *i*-Tartaric acid or
meso-tartaric acid.4. *dl*-Tartaric acid, *r*-tartaric or racemic acid

One of the best known examples of isomeric compounds containing two similar asymmetric atoms is found in the dihydroxy-succinic acids, $\text{HOOC}.\text{CHOH}.\text{CHOH}.\text{COOH}$, which have played a conspicuous part in the history of optical activity. In accordance with theory, these exist as dextro-, laevo-, and *i*- or meso-tartaric acids; and in addition as racemic acid, which has double the molecular weight of the above three forms, and is produced by union of *d*- and *l*-tartaric acids. The dextro- and laevo-acids are optical antipodes, whereas meso-tartaric and racemic acids are inactive. As shown in the formulæ, Figs. 5, 6 and 7, racemic acid is resolvable and meso-tartaric acid non-resolvable. The lack of optical activity in meso-tartaric acid is also revealed by the fact

that the molecular formula (see Fig. 7) possesses a *plane of symmetry*, i.e. a plane dividing the structure into two halves bearing the relationship of object to mirror-image.

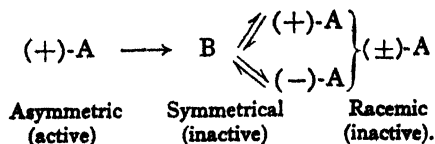
Racemisation

It should be noted that many optically active compounds become more or less completely inactive under the influence of heat or chemical reagents, a process known as *racemisation*. In this way *d*-tartaric acid when strongly heated with water is transformed into a mixture of racemic and meso-tartaric acids.

A number of other acids such as aspartic, mandelic and camphoric acids may be converted into their racemic forms in a similar way. Some compounds (limonene, pinene, amyl alcohol) lose their activity on being merely heated to a sufficiently high temperature; others (tartaric acid, mandelic acid, amyl alcohol and many amino-acids) are slowly racemised when heated with aqueous alkalis; in still other cases (limonene, *d*-valeric acid) sulphuric acid is an active catalyst.

In a few instances the optical activity has been found to disappear spontaneously in the course of time at the ordinary temperature. Walden discovered that esters of optically active bromo-succinic and phenyl-bromacetic acids gradually became inactive during the lapse of several years. This was formerly described as a case of *autoracemisation*. It has since been shown, however, that no racemisation occurs in these esters if they are completely freed from traces of hydrobromic acid.¹ Genuine examples of autoracemisation will be found in 2 : 2'-dibromodiphenyl-4 : 4'-dicarboxylic acid (p. 39) and the oxime of 2-hydroxy-1-acetyl-3-naphthoic acid (β -form, p. 55).

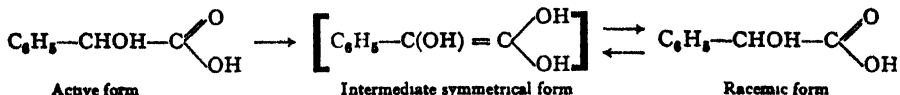
Racemisation appears to be due to the occurrence of some kind of molecular change under the influence of heat or a suitable catalyst, as the result of which an asymmetric molecule A exists temporarily in equilibrium with an isomeric form B (or a simple derivative thereof) which is not asymmetric in structure. The optically active (say, (+)-rotatory) compound A is therefore undergoing constant conversion into the inactive substance B. The molecules of A regenerated from B by the equilibrium process will, however, be composed of an equal mixture of (+)- and (−)-rotatory forms, since in general there is no reason why



one mirror-image isomeride should be produced in excess of the other. In the end, therefore, the whole of the active form A is converted into the racemic compound (\pm)-A. (+)-Mandelic acid, for example, loses its

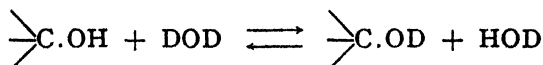
¹ R. Kuhn and T. Wagner-Jauregg, *Naturwissenschaft*, 1929, 27, 103.

activity when heated for several hours with a large excess of aqueous alkali, a change which may occur according to the scheme



On the other hand, many optically active acids which might be expected to undergo this molecular rearrangement retain their activity undiminished under such conditions.

Optically active mandelic acid also undergoes racemisation when heated in water, but an enolisation mechanism is here excluded since if the racemisation is effected in heavy water only two atoms of deuterium are found in the inactive product. This deuteration is an exchange reaction of the type :



Had the planar form postulated above with its three hydroxyl groups been an intermediate in the racemisation process more than two atoms of deuterium would have been taken up.

A remarkably effective reagent for investigating the ease of racemisation of carboxylic esters, acid amides and ketones of the general formula $\text{R}'\text{R}''\text{CH.CO.R}$ was discovered by McKenzie in sodium or potassium ethoxide. The process is a *catalytic* one and systematic studies were carried out¹ by examining the changes, if any, which occur when a small amount of an alcoholic solution of the reagent is added to a solution of the active substance in alcohol. In many cases this leads to complete racemisation within a short time even at room temperature ; in others the optical rotation either changes more slowly or not at all. From the theoretical standpoint every optically active compound of the above general formula may be considered to be capable of undergoing racemisation by existing in equilibrium with the tautomeric form $\text{R}'\text{R}''\text{C}:\text{C(OH).R}$. It has been established by McKenzie, however, that two conditions must be fulfilled before this change can occur in practice. Firstly, as is implied in the above formulæ, the asymmetric atom must be attached to a hydrogen atom and be situated in the α -position to a ketonic group. Secondly, racemisation only takes place if an aromatic group such as phenyl or naphthyl is also united directly to the asymmetric

atom. Thus phenyl-*p*-tolylacetic ester, $\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{CH}_2\text{.C}_6\text{H}_4 \end{array} \text{CH.COOR}$, undergoes rapid racemisation, whereas purely aliphatic acids and esters of corresponding structure retain their activity even on vigorous treatment

¹ A. McKenzie, *J.*, 1915, 107, 704; 1919, 115, 602; Wren, *ibid.*, 1918, 113, 210; A. McKenzie and Miss I. A. Smith, *Ber.*, 1925, 58, 894

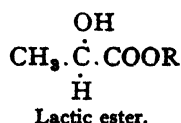
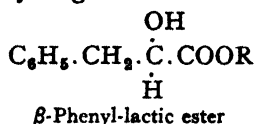
with alkalis. Two other esters which are optically stable in the presence of sodium ethoxide are atrolactic ester,

$$\begin{array}{c} \text{C}_6\text{H}_5 \\ \text{CH}_3 \end{array} \text{C}(\text{OH}) \cdot \text{COOR} \text{ and}$$

β -phenylbutyric ester,

$$\begin{array}{c} \text{C}_6\text{H}_5 \\ \text{CH}_3 \end{array} \text{CH} \cdot \text{CH}_2 \cdot \text{COOR}; \text{ the former because}$$

there is no labile hydrogen atom attached to the asymmetric atom, and the latter because the asymmetric atom is situated in the β -position, so that even if a hydrogen atom in the α -position does migrate it can do so without destroying the asymmetry of the molecule. Similarly, if the phenyl radical in mandelic ester is removed from immediate contact with the α -carbon atom or replaced by an alkyl group, as in the following lactic derivatives, the resulting compounds are not racemised by alcoholic alkali, although they still retain in the α -position an asymmetric atom attached to hydrogen.



The interconversion (*epimerisation*) of acids of the sugar series when heated with quinoline is a racemisation process affecting the α -carbon atom and may be explained in the same manner (see p. 307).

Resolution of Racemic Compounds

Compounds containing asymmetric carbon atoms, which have been prepared synthetically by methods not involving the use of any active substance, are never found to possess optical activity. They generally conform to the racemic type, since in such a synthesis there are always produced equimolecular amounts of the dextro- and laevo-rotatory forms. On the other hand, asymmetric compounds produced with the mediation of living organisms are almost invariably active.¹

Notwithstanding modern research, the methods originally introduced by Pasteur for the resolution of racemic compounds into their optically active components have undergone comparatively little extension. The following are the methods at present available for this purpose.

(a) *Mechanical Separation of the Crystals*.—In a few instances it is possible, by allowing a solution of the racemic mixture to crystallise under certain conditions, to obtain the two enantiomorphs depositing individually—provided they do not form mixed crystals. If, in addition, the crystals possess characteristic differences of the nature of hemihedral facets or striations, it may be possible to separate them by hand.

¹ If a chemical synthesis is effected with the intermediate aid of an optically active substance which is subsequently removed, the product may on occasion also exhibit activity. By means of such *asymmetric syntheses* (p. 41), it is possible to imitate the processes of the living agency.

This method has a very limited application, since the crystallisation of mechanically separable enantiomorphous forms has been observed in very few cases. It was first utilised by Pasteur in 1848 to resolve racemic acid. On crystallising the sodium ammonium salt of racemic acid at a temperature below 27° , it deposits in the form of the corresponding salts of dextro- and laevo-tartaric acids, (+)- and (-)- $\text{NaNH}_4\text{C}_4\text{H}_4\text{O}_6 + 4\text{H}_2\text{O}$; the crystals have different hemihedral facets and may be separated from one another by hand. If the crystallisation is allowed to take place at a temperature above 27° , the *transition temperature*, there separates out unchanged sodium ammonium racemate ($\text{NaNH}_4\text{C}_4\text{H}_4\text{O}_6 + \text{H}_2\text{O}$)₂.

A modification of this method was devised by Ostromisslensky,¹ who showed that supersaturated solutions of the *dl*-compounds, on seeding out with a substance which is isomorphous with the desired active form, can be made to deposit that form exclusively, the other remaining in solution. The success of this method of separation is entirely independent of the presence of an asymmetric carbon atom in the substance with which the solution is seeded. Optically active asparagine, for example, may be precipitated from a supersaturated solution of *dl*-asparagine by the addition of a crystal of glycine, which is itself inactive.

(b) *Resolution by the Biochemical Method.*—This second method of Pasteur is based on the discovery that when lower organisms, such as bacteria, fungi or yeasts, are allowed to grow in a solution containing a racemic compound, the two enantiomorphs are destroyed at different rates (selectively assimilated), so that an excess of one of the active forms accumulates in the solution.² Thus Pasteur found that when *penicillium glaucum* was cultivated in a solution of ammonium racemate, the (+)-tartrate was preferentially destroyed, leaving a solution containing an excess of ammonium (-)-tartrate. In actual practice this method is only of use in comparatively few cases. A useful extension of this method is found in the interaction of an *r*-amino-acid with aniline in the presence of certain enzymes. Aniline reacts only with the amino-acid with the L-configuration (see p. 237) leaving the D-acid untouched. In this way pure D-leucine can be obtained.³ Preferential enzymatic hydrolysis has also successfully been used.⁴

(c) *Resolution by Means of Salt Formation.*—This method depends on the following principle. When a racemic acid A is combined with an optically active, *e.g.* laevorotatory base B, two salts are formed, namely (-)B, (-)A and (-)B(+)A. Such structurally identical but not enantiomorphous compounds with several asymmetric centres are termed **diastereoisomerides**. They possess different solubilities and may be separated by fractional crystallisation or in some cases by chromatographic adsorption (see p. 93). From the individual salts it is then possible to obtain the two active acids. For example, if a solution of

¹ Ostromisslensky, *Ber.*, 1908, 41, 3035. ² A relationship therefore exists between physiological activity and the configuration of chemical compounds. Emil Fischer has shown the influence of configuration on the ability of the monosaccharides to undergo alcoholic fermentation (*Ber.*, 1894, 27, 2035) and on the enzymatic hydrolysis of glucosides. Optical antipodes frequently differ in their action on the animal organism. (-)-Nicotine, for example, is more poisonous than its enantiomorph. See also index under "molecular configuration and physiological activity." ³ M. Bergmann and H. Fraenkel Conrat, *J. Biol. Chem.*, 1937, 129, 707

⁴ B. F. Crowe and F. F. Nord, *J. Org. Chem.*, 1950, 15, 688.

racemic acid be saturated with the optically active base cinchonine, the first salt to crystallise out is cinchonine (—)-tartrate; on the other hand, by employing the base quinine the salt of the (+)-acid is the first to separate. Similarly by union with an active acid, a racemic base may be resolved into its (+)- and (—)-forms. The method may be extended to the resolution of any racemic compound which will unite with acids or bases. In this manner the great majority of resolutions have been effected.

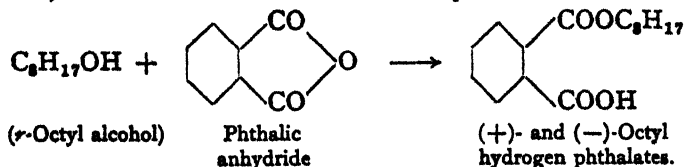
In certain cases a complication arises owing to the *r*-acid combining, for example, with a *d*-base to form the salt (*d*-base, *r*-acid) in addition to the more usual mixture of (*d*-base, *d*-acid) and (*d*-base, *l*-acid). A salt of the first type is termed a **partially racemic compound** (*Ladenburg*).

(d) *Other Resolutions by Means of Active Substances*.—The two components of a racemic acid were shown by Marckwald and McKenzie¹ to esterify at different rates with the same active alcohol. Employing an excess of the racemic acid, the unesterified acid at the end of the reaction was found to be optically active. When, for example, *r*-mandelic acid is incompletely esterified with (—)-menthol, the uncombined residual acid is laevorotatory.

Optically active substances appear in general to react with perceptibly different velocities with the (+)- and (—)-forms of a compound, particularly when the course of the reaction depends in high degree on the constitution of the reagents. A reaction of this type is amide formation, which has also been applied to the resolution of racemic compounds.²

Another method of resolution is that put forward almost simultaneously by Erlenmeyer, jun., and Neuberg. According to Erlenmeyer, a racemic base may be resolved by bringing it into reaction with an active aldehyde. In this way active condensation products termed anils are formed, which are separable by fractional crystallisation. The active base may then be regenerated from the anil by hydrolysis with acids.

Racemic alcohols have been resolved by Pickard and Kenyon by combining them with the anhydride of a strong dibasic acid (succinic or phthalic acid) to form acid esters. For example,



The racemic acid esters (*e.g.* octyl hydrogen phthalates) thus obtained are monobasic acids and can be resolved by use of an alkaloid, usually brucine, after which the individual (+)- and (—)-esters can be hydrolysed to give the optically active alcohols.

¹ Marckwald and McKenzie, *Ber.*, 1901, 34, 469.
² Marckwald and Meth, *Ber.*, 1905, 38, 801.

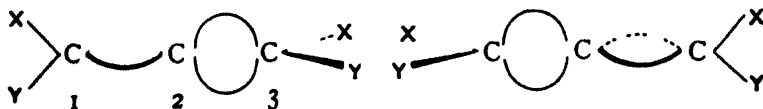
² Marckwald and Meth, *Ber.*, 1905, 38, 801.

Partial resolutions on a micro scale have been effected in one or two isolated cases by taking advantage of the different adsorption coefficients of the (+)- and (-)-components of a racemate for an optically active adsorbent. Thus *r*-*p*-phenylene-bisiminocamphor was partly resolved by Rule and Henderson¹ by adsorbing it from a petroleum-benzene solution on the upper part of a large tube filled with *d*-lactose. The adsorbed layer was then washed with the solvent until it had expanded to fill the tube (compare chromatographic analysis, p. 93). *p*-Phenylene-bisiminocamphor recovered from the upper part of the tube was dextrorotatory, $[\alpha]_{5461} + 485^\circ$ (in CHCl_3), whereas that from the lower part was laevorotatory, $[\alpha]_{5461} - 728^\circ$. The pure active compound has $[\alpha]_{5461} \pm 1975^\circ$. Similar results were obtained by Karagunis and Coumoulos² using the racemic chromium complex, $[\text{Cr}(\text{en})_2]\text{Cl}_3$, on powdered active quartz.

Conditions for Enantiomorphism³

A general condition for the occurrence of a compound in optically active forms is that the molecule should exist in two mirror-image structures which cannot be superimposed one upon the other. In order that this condition may be fulfilled, *it is not essential for the molecule to contain an asymmetric atom* in the strict sense of the definition given on p. 26. A compound possesses the possibility of existing in enantiomorphous forms provided that the configuration of the molecule is devoid of (1) a plane of symmetry, (2) a centre of symmetry and (3) an alternating axis of symmetry.

Plane of Symmetry.—As has already been stated, the space formula of a compound containing an asymmetric carbon atom is without any plane of symmetry. A simple example of a substance containing no asymmetric atom, but for which it is possible to build up two mirror-image and non-superimposable structures, is furnished by allene derivatives of the following type.



If we imagine the terminal group XYC (1) to be in the plane of the paper, then owing to the tetrahedral arrangement of the carbon valencies we must represent the double bond between (1) and (2) as lying in a plane at right angles to that of the paper. The bond between (2) and (3) will then be in the plane of the paper, leaving X and Y (3) disposed, for example, with X behind and Y in front of the plane. As a result of this *spiro*-arrangement (see also *spiro-compounds*, p. 45) the structure possesses no plane of symmetry and cannot be superimposed upon its mirror-image.

Although van't Hoff predicted that compounds of this type should

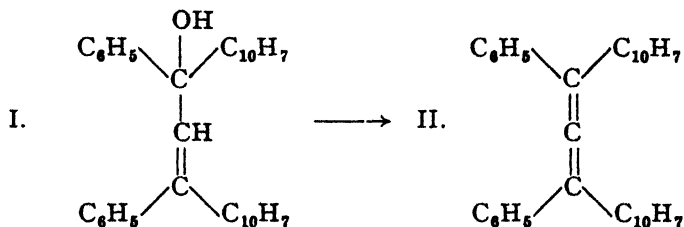
¹ *Nature*, 1938, 142, 917; *J.*, 1939, 1568.

² *Nature*, 1938, 142, 162. See also

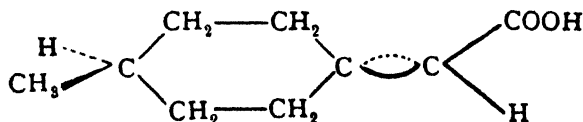
Tsuchida, Kobayashi and Nakamura, *Bull. Soc. Japan*, 1936, ii, 38.

³ The classic paper of Marsh and Barker, *J.*, 1913, 103, 837, should be consulted.

exist in optically active forms, it is only within quite recent times that the possibility has been demonstrated experimentally. In 1935 Mills and Maitland¹ dehydrated the racemic alcohol of formula I by various reagents to give a racemic phenyl-naphthyl-allene II, which melted at 242° to 244°. Dehydration by means of (+)-camphorsulphonic acid, on the other hand, led to the isolation of a strongly dextrorotatory $\alpha\gamma$ -diphenyl- $\alpha\gamma$ -di-1-naphthyl-allene, m.p. 159°, the corresponding laevo-rotatory isomeride of the same melting-point being obtained by use of (–)-camphorsulphonic acid.

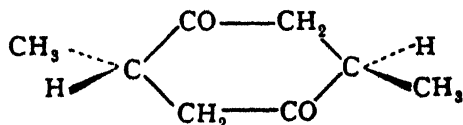


The first successful resolution of a compound containing no asymmetric atom was accomplished by Perkin, Pope and Wallach² (1909) in the case of 1-methyl-cyclohexylidene-4-acetic acid. By recrystallising the



brucine salts of this acid from aqueous alcohol it was separated into two active components. Here also the molecular formula has no plane of symmetry, and two non-superposable mirror-image structures may be built up.

Centre of Symmetry.—Interesting examples of a new class of inactive and indivisible compounds were discovered among the *trans*-diketo-hexamethylenes (Ladenburg) and the *trans*-diketo-piperazines (Fischer). If in the annexed formula we assume the 6-membered rings to lie in the plane of the paper, then the similar *trans*-substituents (*e.g.* CH₃) must be disposed one behind and one in front of this plane. These compounds

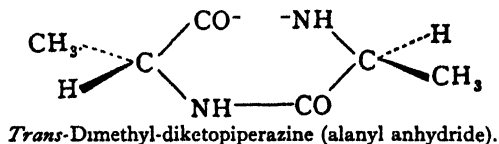


Trans-Dimethyl-diketo-hexamethylene.

each possess two similar asymmetric atoms, but are not of the true meso type since there is no plane of symmetry. Nevertheless, experiment has

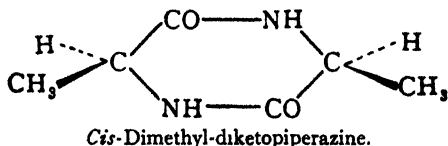
¹ W. H. Mills and P. Maitland, *J.*, 1936, 987. See, however, P. Maitland, *Ann. Reports*, 1939, 239. For the resolution of a carboxylic acid of allene type see E. P. Kohler, J. T. Walker and M. Tishler, *J.A.C.S.*, 1935, 57, 1743. ² *J.*, 1909, 95, 1789.

shown that compounds of this kind cannot be resolved into active components. The real criterion of asymmetry is the configuration of the molecule as a whole, and not the relationship existing between two or more atoms within the molecule. *On building up the mirror-image of one of the above structures it will be found to be identical with the original ;*



there is therefore no possibility of optical isomerism. A close inspection of the formulæ shows that a line drawn from any atom or group to a point in the middle of the ring will, if produced further, meet a similar atom or group. Such a point is known as a *centre of symmetry*.

The existence of a centre of symmetry is therefore sufficient to destroy the possibility of optical isomerism. Ladenburg described the case of *trans*-dimethyl-diketohexamethylene as one of pseudo-symmetry.



In the *cis*-compounds of the above types there is neither a plane nor a centre of symmetry. The *cis*-diketo-piperazines have been found to occur in optically active forms.

Alternating Axis of Symmetry.—Compounds possessing an alternating axis of symmetry are such that on rotating any atom or group round the axis through an angle of 90° , it will, on being reflected across the horizontal plane perpendicular to the axis, come into superposition with a corresponding atom or group. This condition also holds for every successive rotation of 90° . In such cases similar atoms or groups alternate above and below the plane of reflection and the molecule can be superimposed on its mirror-image. This type of symmetry is rarely met with. It occurs, for example, among certain substituted cyclobutane derivatives, in which the alternating axis of symmetry is perpendicular to the plane of the ring and the latter corresponds to the plane of reflection. (For examples see Barker and Marsh.¹)

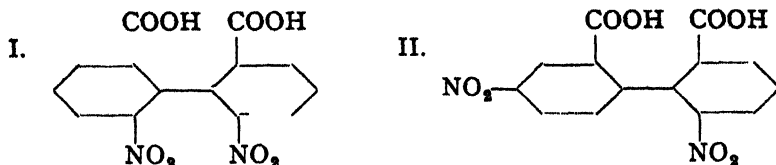
Optical Isomerism due to Restricted Rotation about a Single Bond²

Optical isomerism of a new kind was found to exist in the diphenyl series (p. 547). This development arose from the discovery of Christie

¹ *J.* 1913, 103, 837.

² For a general survey see R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, 22, 261.

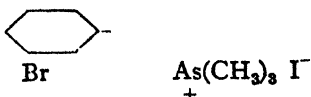
and Kenner that it was possible to resolve substituted diphenic acids, such as the 6:6'- and 4:6'-dinitro-derivatives (I and II) into their optical isomerides.



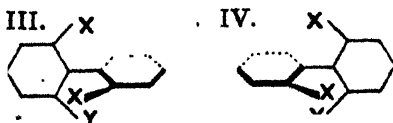
Since then a number of substituted diphenic acids have been resolved,¹ and others shown to be incapable of resolution. Meisenheimer extended the work to basic derivatives such as 6:6'-diamino-*o*-ditolyl, which also exists in enantiomorphous forms.

At first it was believed to be an essential condition for optical isomerism in the diphenyl series that at least three of the four positions adjacent to the bond joining the two benzene nuclei should be occupied by substituents. Later, the resolution of certain di-ortho-substituted compounds such as diphenyl-2:2'-disulphonic acid² and 2:2'-diiododiphenyl-4:4'-dicarboxylic acid proved that only two *o*-substituents were necessary, provided they were sufficiently large. Compounds of this type, however, are comparatively easily racemised by heating, and the ease of racemisation increases when iodine in the above acid is replaced by the smaller substituent bromine. The corresponding dichloro-compound has not yet been resolved.

There is evidence of restricted rotation in the arsonium salt shown below.³ It would appear that a sufficiently bulky 2-substituent is sufficient to prevent coplanarity.

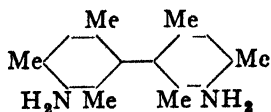


An explanation of this type of isomerism was suggested in the theory of restricted rotation, which was advanced independently by Turner and Le Fevre, Bell and Kenyon, and Mills. It is supposed that the free rotation of the benzene nuclei round the bond uniting them is restricted or altogether prevented by the presence of the substituents in the ortho-positions. If free rotation is inhibited, it is then possible to build up two non-superimposable mirror-image forms for each of the above compounds (*e.g.* III and IV). In other words, the molecules are co-axial but not co-planar.



¹ McAllister and Kenner, *J.*, 1928, 1913; F. Bell and J. Kenyon, *Chem. and Ind.*, 1925, 45, 864. ² Miss M. S. Lesslie and E. E. Turner, *J.*, 1932, 2394. ³ M. S. Lesslie and E. E. Turner, *J.*, 1933, 1588.

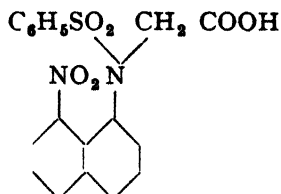
The probability of this explanation becomes evident when actual space models of these derivatives are examined. It is then seen that the benzene nuclei are interlocked. The actual nature of the force preventing rotation is still an open question; it may be a purely mechanical obstruction or electropolar forces may be involved. But the success of Moyer and Adams¹ in resolving 3:3'-diaminodimesityl, in which the four ortho groups are identical and practically non-polar, supports the theory of mechanical blocking. The same conclusion is indicated by the fact that



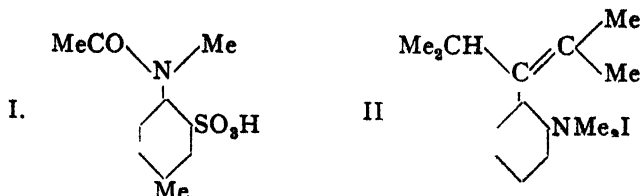
the series $\text{Br} > \text{Cl} > \text{O} \longrightarrow \text{F}$ represents not only the relative blocking powers of the substituents but also their relative atomic diameters.

The case of 6:6'-dinitro-diphenic acid illustrates the fact that complete asymmetry is not an essential condition for optical isomerism, since the compound occurs in two non-superposable forms. As in many other cases, the molecular structure of this compound possesses certain elements of symmetry and is therefore described as *dissymmetric* rather than asymmetric.

Optical isomerism due to restricted rotation round a single bond would be expected to occur in other compounds besides the diphenyl group. Further support for the theory was furnished by Mills and Elliot in resolving the benzenesulphonyl derivative of 8-nitro-1-naphthylglycine. In this case the optical isomerides are unstable, and the rotatory power disappears in the course of a few hours (autoracemisation). In the absence of the nitro group no isomerism occurs.



Simple benzene derivatives exhibiting optical activity of this type have been discovered by Mills and co-workers in the compounds I and II.

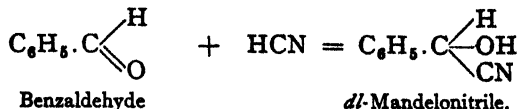


Compound I was found to undergo slow racemisation, the activity of the sodium salt falling to zero over a period of some hours. If the sulphonic group is replaced by the less bulky carboxyl group, however, no resolution can be effected. The active iodides of structure II showed great optical stability, but here also all optical isomerism disappeared when hydrogen was substituted for one of the relatively bulky methyl groups ($\text{C}=\text{CMe}_2 \longrightarrow \text{C}=\text{CHMe}$).

¹ W. W. Moyer and R. Adams, *J.A.C.S.*, 1929, 51, 630.

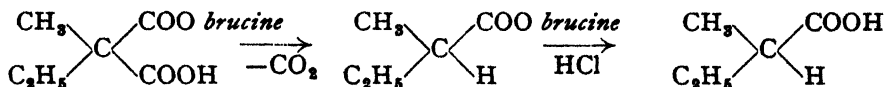
Asymmetric Synthesis

It has already been stated that when a symmetrical compound is converted by ordinary chemical reaction into one of asymmetric type, the new product is not optically active but is of the racemic variety, *e.g.*



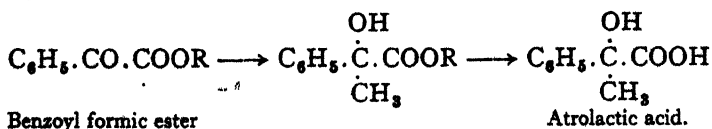
The ordinary chemical and physical properties of the optical isomerides (*e.g.* the (+)- and (−)-mandelonitriles in the above equation) are identical and there is no reason why the one form should be produced in greater amount than the other. If, however, such a reaction is carried out under the influence of an optically active grouping which is subsequently removed, the product may be found to exhibit optical activity. A synthesis of this kind is termed an *asymmetric synthesis*.

Marckwald in 1904 claimed to have effected the first asymmetric synthesis by preparing an active (−)-valeric acid from the acid brucine salt of methyl ethyl malonic acid, by heating the latter at 170°. The



actual mechanism by which active valeric acid is formed in these reactions has been the subject of discussion. Recent work supports the view that the process is not a true asymmetric synthesis, but that the activity of the final product depends on the fact that the deposition of the crystalline acid brucine salt (which contains a newly created asymmetric C-atom in the malonic residue) is accompanied by a displacement of the equilibrium of the two diastereoisomerides in accordance with their differing solubilities. Thus the solid salt before decomposition by heat does not contain brucine hydrogen (+)-methyl-ethylmalonate and brucine hydrogen (−)-methyl-ethylmalonate in equal amounts.

In the same year A. McKenzie prepared a laevorotatory atrolactic acid by treating (−)-menthyl benzoylformate with one molecular proportion of methyl magnesium iodide, and subsequently removing the menthyl grouping by hydrolysis.



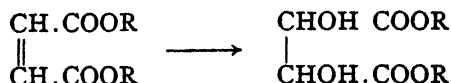
The following asymmetric syntheses are also due to McKenzie and his co-workers.

When an ester of pyruvic acid is reduced, it is converted into a lactic ester, with the simultaneous creation of an asymmetric atom. By reducing

(-)-menthyl or (-)-bornyl pyruvates in an aqueous solvent with aluminium amalgam, McKenzie obtained lactic esters which on hydrolysis gave a lactic acid containing an excess of (-)-acid. Similarly the (+)-amyl ester led to the formation of an excess of (+)-lactic acid,



A further asymmetric synthesis effected by McKenzie and Wren is based on the oxidation of fumaric acid to racemic acid by means of potassium permanganate.¹ The oxidation of (-)-bornyl fumarate pro-



duced a mixture of (+)- and (-)-tartaric esters containing an excess of bornyl (-)-tartrate, and on removing the bornyl group a laevorotatory tartaric acid was obtained. By using (+)-bornyl fumarate an excess of (+)-tartaric acid was formed.

Rosenthaler showed that the combination of aldehydes with hydrogen cyanide in the presence of enzymes gives rise to active cyanhydrins. Benzaldehyde and HCN in the presence of emulsin yield optically active (+)-mandelonitrile, which on hydrolysis gives an active (-)-mandelic acid. Similar results were obtained by Bredig and Fiske, who used optically active alkaloids in place of enzymes. Quinine, for example, gives a laevorotatory mandelonitrile and quinidine a dextro-rotatory product.

Many attempts have been made to produce optically active substances by generating asymmetric compounds under the influence of circularly polarised light or an asymmetric arrangement of polarised light and magnetic field. The former method was suggested independently by Le Bel and van't Hoff and has recently been realised experimentally. Karagunis stated that triarylmethyls containing three different groups attached to the central carbon atom (CR'R''R''') combine with bromine or chlorine under the influence of *d*-circularly polarised light to form very weakly laevorotatory triarylmethyl halides. With *l*-circularly polarised light the rotation is dextrorotatory.

Asymmetric Decomposition

A somewhat different procedure has been advocated by Cotton, who discovered that copper (+)- and (-)-tartrates in alkaline solution exhibit circular dichroism, a *d*-circularly polarised ray, for example, being more strongly absorbed by the (+)-salt than by the (-)-compound (*Cotton effect*). Hence Cotton tried to decompose a solution of the racemate with *d*-circularly polarised light in the hope of obtaining a mixture containing an excess of (-)-tartrate. No activity could be observed, however. After

¹ It may be noted that maleic acid on oxidation yields mesotartaric acid

many fruitless attempts along these lines on the part of various investigators, success was finally achieved by Werner Kuhn,¹ and S. Mitchell.² Kuhn made use of *dl*- α -azidopropionic dimethylamide, $\text{CH}_3\cdot\text{CHN}_3\cdot\text{CO}\cdot\text{N}(\text{CH}_3)_2$. This was found to have an absorption band due to the azido-group, situated in the ultra-violet region at $\lambda = 2900 \text{ \AA}$, in the neighbourhood of which the rotation rose enormously. On passing *d*-circularly polarised light of the same order of wavelength (chiefly $\lambda = 3135$) through the solution, decomposition ensued with the liberation of nitrogen, the recovered dimethylamide having the rotation, $\alpha_{5780} = +0.78^\circ$ ($l = 1$). When *l*-circularly polarised light was employed the product had $\alpha_{5780} = -1.04^\circ$.

The asymmetric photochemical decomposition of humulene nitrosite effected by Mitchell has the merit of simplicity, since it was brought about by the use of visible light in the red part of the spectrum (6000–7800 \AA .U.), and the change could be followed throughout by polarimetric readings. Humulene is an inactive sesquiterpene which combines with nitrous anhydride to form a racemic nitrosite. A solution of the latter in ethyl butyrate on being irradiated with *l*-circularly polarised light of the above wavelength showed a gradually increasing (+)-rotation (maximum value $\alpha_{5780} = +0.30^\circ$) which eventually fell during the course of sixty-four hours to zero, by which time the decomposition of the nitrosite was complete. Similar rotations of the opposite sign were obtained in a parallel experiment with *d*-circularly polarised light.

These syntheses of active compounds from racemic material are not asymmetric syntheses in the usual sense of the word but are akin to Pasteur's resolutions with bacteria or moulds, which feed preferentially on one of the active forms in a solution of the racemate.

The causes which first led to the formation of optically active compounds in nature have been the subject of much speculation. The successful photochemical decompositions outlined above indicate one possible solution of the problem, since ordinary daylight is well known to contain under certain conditions a small proportion of circularly polarised light. But whatever the original source of the activity, it is probable that the great majority of highly active substances now elaborated by animal and vegetable organisms are formed by asymmetric syntheses under the influence of optically active enzymes or other products (alkaloids, carbohydrates, etc.) already present in the organism.

B. GEOMETRICAL ISOMERISM

The tetrahedra representing two carbon atoms united by a single bond are in contact at one point only, and capable of independent rotation about their common axis. If this were not so, even the simplest compound of this type, such as ethane, $\text{H}_3\text{C}-\text{CH}_3$, should exist in innumerable

¹ W. Kuhn and E. Knopf, *Zeit. phys. Ch.*, 1930, B, 7 (4), 292.

² Mitchell, *J.*, 1930, 1829.

modifications. There is, however, only one ethane known. Stereoisomerism is therefore not possible with ethane derivatives unless the carbon atom is asymmetric. As suggested by Wislicenus, it is probable that the atoms or groups united to the two carbon atoms exert a mutual directive influence on each other, until by rotation about the common axis the whole system is transformed into the most stable configuration.

The case is otherwise with doubly bound carbon atoms as contained in ethylene derivatives of the general formula $abC:Ccd$. All independent turning of the tetrahedra ceases here, since two corners of each are in union, with a whole edge in contact and the remaining four valency bonds lying fixed in one plane. This picture of olefinic compounds is confirmed by the X-ray study of dimethyl fumarate which shows it to be planar or nearly so.

For this reason compounds of the formula $abC:Cab$ (and also of the general structure $abC:Ccd$) exist in two stereoisomeric forms, corresponding to the configurations :

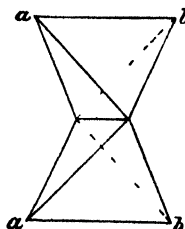


FIG. 8.

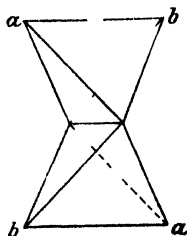
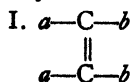
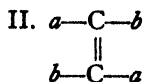


FIG. 9.

By projection on to a plane parallel to that containing the four radicals, these formulæ may be simplified to

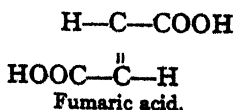
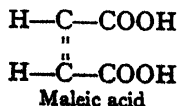


and



Compounds of configuration I, in which similar groups lie on the same side of the molecule, are known as *cis*-forms; they possess one plane of symmetry perpendicular to the axis of the double bond, and another containing C, *a*, *b* and the double bond. Those of configuration II, with similar groups on opposite sides, and having one plane of symmetry containing the axis of the double bond are known as *trans*-forms.

The best known illustration of this type of isomerism is furnished by maleic and fumaric acids :



In maleic acid the two carboxyl groups lie on the same side of the molecule (*maleinoid* position), and in fumaric acid on opposite sides (*fumaroid* position). The compounds differ not only in physical but

also in chemical behaviour (see p. 289). Maleic acid, for example, owing to the proximity of the carboxyl groups, readily forms a stable anhydride, a change not possible in the case of fumaric acid. When strongly heated, fumaric acid is partially transformed into water and the anhydride of maleic acid.

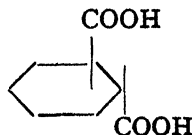
Geometrical isomerism is a common occurrence among those ethylene derivatives in which two different groups are united to each doubly bound carbon atom. Into this class fall the two dimethylethylenes, $\text{CH}_3\cdot\text{CH}:\text{CH}\cdot\text{CH}_3$, crotonic and isocrotonic acids, $\text{H}_3\text{C}\cdot\text{CH}:\text{CH}\cdot\text{COOH}$, angelic and tiglic acids, $\text{CH}_3\cdot\text{CH}:\text{C}(\text{CH}_3)\cdot\text{COOH}$ and many others.

Under certain conditions the geometrical isomers of the ethylene series are interconvertible; thus by heating maleic acid in aqueous solution with a small amount of hydrochloric acid, it is converted into fumaric acid.

A similar geometrical isomerism is found among the cyclic polymethylene compounds, despite their saturated character. In this case, the closed structure of the ring inhibits axial rotation of the carbon atoms in the same manner as the double bond of ethylene derivatives.¹ A comparatively large number of isomerides of this class is known, including the hexahydrotetraphthalic acids, and the quinitols, $\text{C}_6\text{H}_{10}(\text{OH})_2$. The existence of isomerism is explained in the same way by assuming that certain groups in the compound may occupy opposing positions in space, in the sense that they may in one case be in proximity, and in the other be removed from one another. A foundation for this explanation is provided by the fact that the one isomer frequently undergoes intramolecular reactions which appear to necessitate neighbouring positions of the groups involved, whereas the other isomer does not undergo these reactions at all. The two hexahydrophthalic acids, for example, exhibit the same relationship as maleic and fumaric acids, as indicated in the following diagrams. The *cis*-acid readily forms an anhydride; whereas the *trans*-anhydride, which is only obtained with difficulty, is converted on fusion into the stable *cis*-anhydride. This change involves a rearrangement of the groups.



Maleinoid or *cis*-acid.



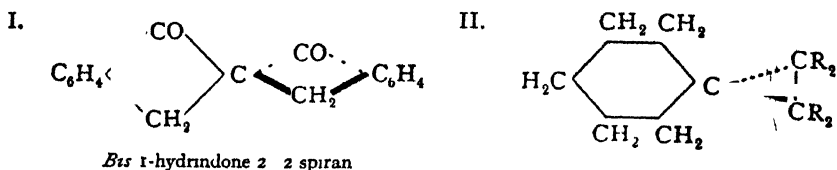
Fumaroid or *trans*-acid.

Spirocompounds

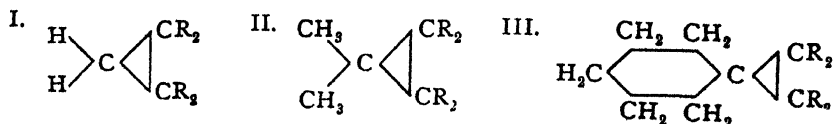
Closely related to the allene derivatives mentioned on p. 36 are the **spirans** or **spiro-compounds**. Spirans are cyclic compounds built up

¹ It is also possible to consider ethylene as the simplest example of a molecule with ring structure.

of at least two homo- or hetero-cyclic rings, and having one ring-atom common to both cyclic structures (I and II). Owing to the tetrahedral arrangement of the bonds around the common atom,¹ the two rings may be regarded as occupying planes at right angles to each other. In many cases the spatial disposition of the groups leads to the occurrence of stereoisomerism.

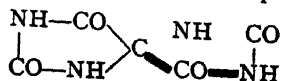


An extensive investigation was carried out by Thorpe, Ingold and co-workers on the formation and stability of spiro-compounds. It is well known that in cyclopropane the distortion of the valency bonds from the normal is so great that derivatives of this hydrocarbon are not readily formed and are unstable. The above authors have shown that the ease of formation of the cyclopropane ring is increased when the CH₂



group in I is replaced by the *gem*-dimethyl group as in II and to a still greater degree by the cyclohexane group as in the spiro-compound III. It is therefore concluded that in the simple cyclopropane ring (in which the bonds are calculated to enclose an angle of 60°, as compared with the normal value of 109°28' for methane) the strain between the carbon bonds is lessened by the introduction of the bulky *gem*-dimethyl group, CH₃, or the cyclohexane residue. In the last two cases the widening of the angle between two of the bonds by space-filling groups may be assumed to bring about a decrease in the angle enclosed by the remaining two bonds, thus facilitating the closure of the ring. Once it is formed, the ring in these last-named compounds is under less strain and hence is less liable to disruption.

The resolution of *spiro*-5-5-hydantoin by Pope and Whitworth furnishes a remarkably simple example of an optically active spiran.



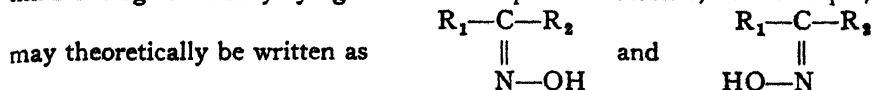
2. Stereochemistry of Nitrogen

(a) Optical Isomerism

The frequent occurrence of oximes and hydrazones, all of which contain the group >C:N—, in geometrically isomeric forms, has been explained by Hantzsch on the assumption that the nitrogen and carbon

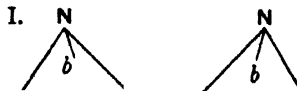
¹ This holds for N as well as C; compare stereochemistry of nitrogen, p. 50.

atoms lie in the same plane as the double bond joining them, with the third nitrogen valency lying outside this plane. Oximes, for example,

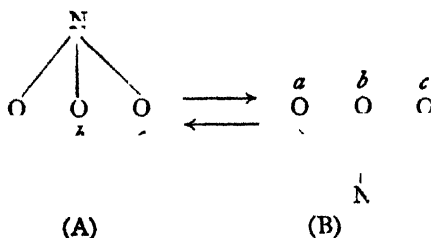


and in many cases both forms have been isolated (see p. 52 *et seq.*).

If the three nitrogen valencies were arranged in this way in trivalent nitrogen compounds of the type $Nabc$, the latter would be expected to occur in optical isomerides as in I. Many attempts have been made to resolve such compounds but without success. For example, no resolution could be effected in the case of benzyl-ethyl-amine, β -benzyl-hydroxylamine, methylaniline, tetrahydroquinoline, or hippuric acid by means of active acids. It is of interest, however, that a diamine, *Tröger's base*, has been obtained in the optically active form.¹



It has therefore been concluded that these compounds $Nabc$ do not occur in stable enantiomorphous forms. The fact that ammonia and similar compounds have a definite dipole moment (see p. 72) proves that the three radicals a , b and c do not lie in the same plane as the nitrogen atom. The system is therefore assumed to be mobile so that racemisation occurs by the nitrogen atom vibrating through the plane of the attached groups (a , b , c). A is thus converted into its enantiomorph B and *vice versa*.



(b) Optically Active Ammonium Salts

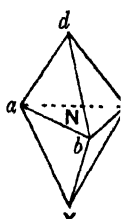
Corresponding to the asymmetric atom of carbon we have that of pentavalent nitrogen, the five bonds of which are united to different atoms or groups. A configuration of this type is represented by the substituted ammonium salts $N(a, b, c, d)X$, which would therefore be expected to exist in two optically active forms of equal and opposite rotation, and an inactive racemic form containing equimolecular amounts of these two isomers.

In confirmation of this, Le Bel obtained methyl-ethyl-propyl-isobutyl ammonium chloride, $N(CH_3)(C_2H_5)(C_3H_7)(C_4H_9)Cl$, in a feebly active state by submitting a solution of the salt to the action of the mould *penicillium glaucum*. Pope and Peachey (1899) prepared

¹ V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1944, 27, 1127

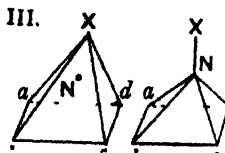
the *benzyl-phenyl-allyl-methyl ammonium salt* of (+)-camphorsulphonic acid, and by fractional crystallisation from the non-hydrolysing solvents ethyl acetate and acetone succeeded in resolving it into its enantiomorphous forms. The individual (+)-camphorsulphonates, on treatment with potassium iodide, gave the sparingly soluble substituted ammonium iodides of $[\alpha]_D = +52.5^\circ$ and $[\alpha]_D = -51.4^\circ$ respectively. These were the first optically pure compounds to be prepared, the activity of which was due to an element other than carbon.

Earlier work on the isomerism of nitrogen compounds led to the consideration of two space arrangements for the pentavalent nitrogen atom. In one of these, due to Willgerodt, the five bonds were assumed to lie at the points of a figure obtained by placing two tetrahedra base to base (II).



The nitrogen atom was supposed to lie inside the common triangular base, $a b c$, with Na , Nb and Nc representing the valencies of the original trivalent nitrogen. Willgerodt's arrangement was subsequently abandoned because it permits a far greater number of isomerides than is actually found in practice, viz., two different optically inactive isomerides Na_3bX , three isomerides of Na_2bcX (one of which should be resolvable) and four resolvable forms of $NabcdX$.

The second formula for ammonium compounds, due to Bischoff, represented the N-atom as lying inside a square pyramid $Xabcd$ (III), with four valencies directed towards the points of the square base and the ionising valency towards the apex. This also requires a greater number of isomerides than has been observed. For example, compounds of the type $NabccX$ should exist in two forms, one of them resolvable (IV) and the other non-resolvable (V). Similarly, $NabcdX$ should occur in three resolvable forms.



The experimental evidence on which the formulæ have to be judged is somewhat conflicting. There are many cases of dimorphism among these salts and in a number of instances supposed isomers have been shown later to be identical. The main facts may be summarised as follows. No optical isomerism has been observed in compounds of the types Na_3bX or Na_2bcX . Compounds of the type $NabcdX$ occur in a single resolvable form, and the same racemic compound is produced whatever the order in which the radicals a , b , c , d are introduced into the molecule.

IV.

V

N

b

As further examples of the large number of compounds $NabcdX$ resolved by Pope, Wedekind, H. O. Jones and others, may be mentioned those built up of phenyl, methyl, benzyl and a series of alkyl radicals, and the cyclic compound, allyl kairolinium iodide (VI).

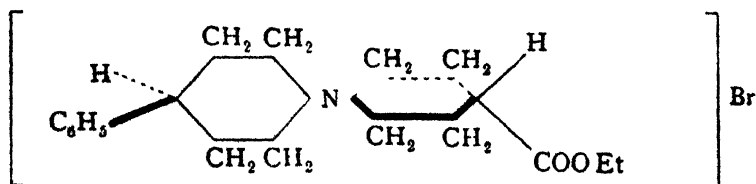
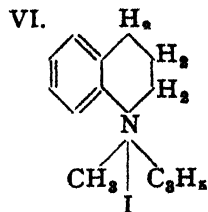
For some years the Bischoff formula was considered to be in best agreement with the experimental facts. Later it became recognised that *the fifth or ionisable valency of nitrogen has no fixed direction with respect to the rest of the atom and is therefore without influence on the asymmetry.*

This was first expressed by Werner,¹ who formulated ammonium salts with the ionisable group occupying an outer zone and the four radicals in an inner zone. Werner suggested that the stereochemistry of nitrogen thus resembled that of methane, one atom being present in a positively charged ammonium ion and the other in an electrically neutral molecule.

According to modern views the two ions of an ammonium salt are regarded as separate entities, normally held together by the electrostatic attraction of oppositely charged bodies. The individuality of the ions appears to be maintained even in the solid state. Wyckoff, from the X-ray examination of crystals of ammonium chloride, concludes that they are built up of an aggregate of alternating ammonium and chloride ions.

An interesting decision in favour of the tetrahedral as against the pyramidal formula for the ammonium ion was obtained by the success of Mills and Warren in resolving the following spiro-compound (see below) into its optical isomerides.

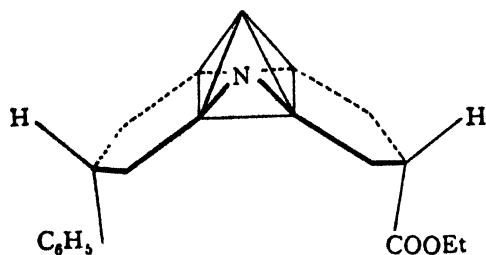
The formation of this compound from 4-phenylpiperidine and $\alpha\epsilon$ -dibromopentane- γ -carboxylic ester took place very readily, and it is therefore assumed that the valency bonds of the nitrogen atom are disposed normally and are not under strain. If the arrangement



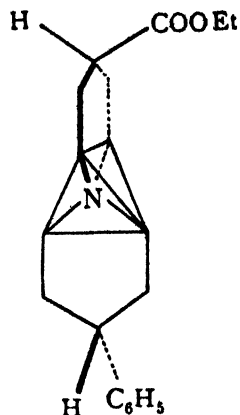
4-Phenyl-4'-carbethoxy-bis-piperidinum-1:1'-spiran-bromide.

of the N-bonds is tetrahedral, as indicated in the above formula, then the compound is asymmetric, because the two rings must lie in planes perpendicular to one another, thus bringing the terminal

¹ *Z. anorg. Ch.*, 1906, 19, 1352. *New Ideas on Inorganic Chemistry*, p. 53.

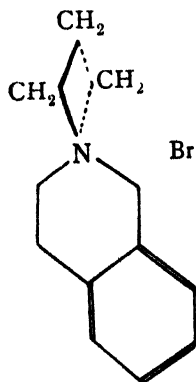


Pyramidal formula



Tetrahedral formula.

substituents, C_6H_5 , H and $COOEt$, H also into planes at right angles to one another. On the Bischoff formula, on the other hand, the compound is symmetrical since in this case the terminal groups lie in one plane which is at right angles to the planes of the two similar rings. The resolution was effected by recrystallising the *d*-bromo-camphorsulphonates from acetone.



The tetrahedral arrangement of the nitrogen valencies also explains the failure of other workers to resolve compounds such as the trimethylene tetrahydroisoquinolinium salts. On the tetrahedral arrangement the plane containing the isoquinoline rings will cut the trimethylene group at right angles, dividing it into two equal halves and thus constituting a plane of symmetry, as may be seen from the foregoing figure. On the pyramidal formula of Bischoff the compound is asymmetric in structure and should be resolvable.

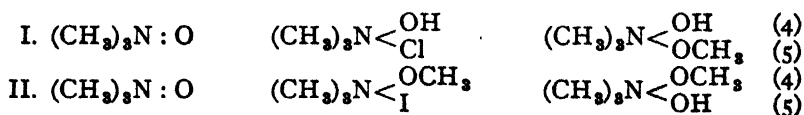
The Inequality of the Five Valencies of Nitrogen

It has been shown by Meisenheimer¹ that the pentavalent nitrogen compound methyl-ethyl-aniline oxide $(CH_3)(C_2H_5)(C_6H_5)N=O$, which is prepared by treating the amine with hydrogen peroxide, exists in two optically active forms, despite the apparently identical state of combination of two of the nitrogen bonds. Similar isomerism is exhibited by methyl-ethyl- β -naphthylamine oxide and by kairolin oxide, a cyclic amine oxide.

We may therefore assume that all amine oxides, $Nabc(:O)$, containing a nitrogen-oxygen double bond and three different alkyl radicals attached

¹ Meisenheimer, *Ber.*, 1908, 41, 3966. *Ann.*, 1911, 385, 117; 1913, 397, 273; 399, 371.

to the nitrogen are capable of existing in two enantiomorphous forms, although, as indicated by the experiments of Jones, similar compounds of the type $NaabcX$ or $N(:a)bcX$ in which the double bond lies between nitrogen and carbon cannot be resolved into active isomerides. This was explained by assuming that in the latter compounds the valencies of the double bond, or those united to the two similar radicals, are incapable of binding ionisable groups, whereas in the amine oxides the valency formerly bound to the ionisable acidic group participates with one of the four remaining valencies in the double bond. A fundamental assumption of this theory is the inequality of the five nitrogen valencies in ammonium compounds, it being supposed that the fifth bond, uniting ionisable groups, was of a different nature. The probability of this hypothesis was strengthened by the discovery of Meisenheimer that in compounds of the type $(CH_3)_3NCl_2$, or $(CH_3)_3N(OH)_2$, the chlorine atoms or hydroxyl groups are in different states of combination. For example, two different substances of the formula $(CH_3)_3N(OH)(OCH_3)$ are produced according as a salt of trimethylamine oxide is treated with sodium methoxide (I) or the addition compound of trimethylamine oxide with methyl iodide is decomposed by sodium hydroxide (II).



The trimethyl-hydroxy-ammonium methoxide formed in reaction I, quantitatively decomposes into methyl alcohol and trimethylamine oxide on evaporating the aqueous solution. The trimethyl-methoxy-ammonium hydroxide produced in reaction II, on the other hand, yields trimethylamine, formaldehyde and water. In addition to the above, several pairs of isomers of the type $(CH_3)_3N(OR')(OR'')$ were isolated. All of these could be decomposed to give trimethylamine, aldehyde and alcohol; in each case the alkyl residue occupying position (4) was liberated as aldehyde, and no trace of any other aldehyde could be detected. It follows, therefore, that the two alkoxy groups are not linked to nitrogen in the same manner. Meisenheimer assumed the five radicals to be attached to nitrogen by means of principal valencies, four in an inner and one in an outer zone (III and IV) as in Werner's theory.



It was supposed that the group in the outer zone, at all events when the substance is in solution, resembled the labile group of a tautomeric compound in having no fixed position, and had therefore no apparent influence on the asymmetry of the molecule.

An explanation of the constitution of the amine oxides has been advanced by Lowry and Sidgwick (see p. 20) on the basis of the electronic theory.

(c) Geometrical Isomerism of Nitrogen Compounds

All nitrogen compounds capable of exhibiting geometrical isomerism are characterised structurally by a double bond between carbon and nitrogen, and the isomers bear the same relationship to one another as those of the ethylene series (p. 44).

Starting from the consideration that numerous compounds are known in whose molecule a N-atom plays the equivalent part of a CH-group (*cf.* benzene and pyridine, naphthalene and quinoline), Hantzsch and Werner suggested that the three valencies of the nitrogen atom are directed towards three summits of a tetrahedron, at whose fourth lies the nitrogen atom itself. Hence all compounds containing the divalent group $a-C-b$ united to the divalent $N-c$ should, by analogy with the ethylene derivatives, occur in two different configurations :



or representing the nitrogen compounds in perspective,

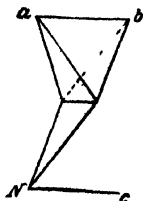


FIG. 10.

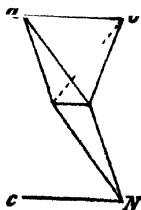
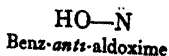
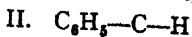
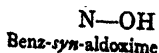
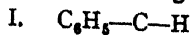
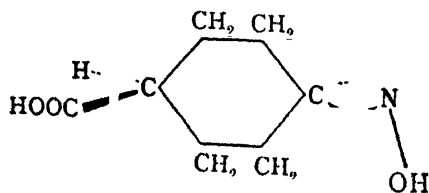


FIG. 11.

One of the most important and earliest investigated classes of this type is that of the oximes; inquiry was later extended to the hydrazones, carbazones and imides. The two isomeric benzaldoximes, for example, are given the configurations I and II following :



Strong confirmation of this theory is provided by the success of Mills



and Bain in resolving the oxime of cyclohexanone carboxylic acid into optically active forms. The asymmetry of the compound can only be explained on the assumption that the hydroxyl of the oxime

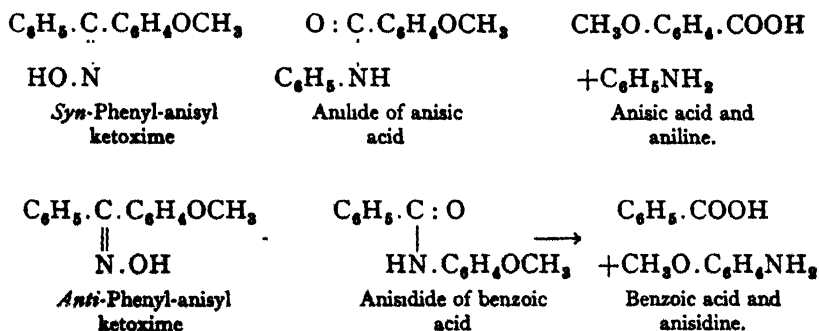
group lies in a different plane to that occupied by the H and COOH at the other end of the molecule.

In agreement with the above theory, the symmetrical ketones, R_2CO , yield only one oxime, and the unsymmetrical ketones, $R'R''CO$, yield in

general two, although in some cases only one is known, the other being apparently too unstable to be isolated. Similarly, a symmetrical diketone such as benzil, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CO}\cdot\text{C}_6\text{H}_5$, forms two monoximes and three dioximes.

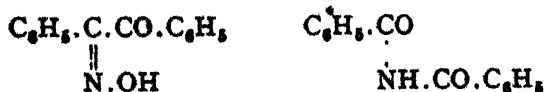
The *configurations of stereoisomeric aldoximes* were first deduced by methods devised by Hantzsch. One form readily loses water to yield a nitrile, whereas the other is more stable. It was therefore concluded that the former was probably a *syn*-aldoxime, with H and OH in close spatial proximity; and that the latter was an *anti*-aldoxime, with H and OH on opposite sides of the molecule. Still greater differences in ease of nitrile formation are shown by the acetyl derivatives of the oximes (p. 189).

Hantzsch deduced the *configurations of the ketoximes* by means of the Beckmann transformation (p. 190), which may be effected, for example, by treating the ketoxime in benzene or ether solution with phosphorus pentachloride, when it is converted into a substituted amide. The two isomers yield different products, and Hantzsch assumed that the change occurred in the following manner, the hydroxyl group being supposed to exchange places with the adjacent radical in the *cis*-position, followed by a rearrangement to the substituted amide. As an example we may quote the case of the phenyl anisyl ketoximes.¹



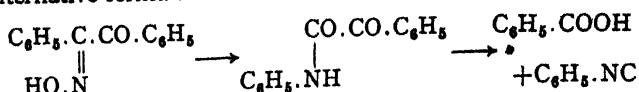
The constitution of the final product is then determined by hydrolysis to the acid and amine.

By a similar method, configurations were assigned to the two monoximes of benzil. The α -form, m.p. 140° , yields dibenzamide as sole product of the Beckmann transformation and was therefore given the following structure :

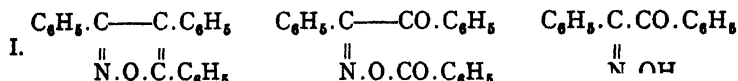


¹ In the aldoximes the prefix *syn*- indicates adjacent positions of the reactive groups H and OH. In the ketoximes the term *syn*- or *anti*- indicates the position relative to OH which is assumed by the group immediately following the prefix.

The β -form, m.p. 113° , was found to be converted through benzoyl-formanilide into phenyl isocyanide and benzoic acid. It was thus given the alternative formulation :

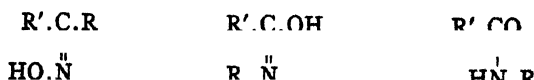


In deriving stereochemical formulæ from an examination of intramolecular reactions such as these, it was at first assumed that the changes would proceed all the more readily the closer the reacting groups are to one another in space. Unfortunately, no facts were known by which the validity of this assumption could be strictly tested in the case of the oximes, and there has always remained the possibility that the Beckmann rearrangement, for example, does not involve an interchange of adjacent groups, but of groups in the *anti*-position. The whole question of the configuration of aldoximes and ketoximes was reopened by the discovery of reactions which reversed the accepted structures.¹ Meisenheimer found that when triphenylisoxazole (I) is oxidised with ozone or chromic oxide, there is obtained a benzoylated benzil monoxime which on hydrolysis yields a benzil monoxime. We should expect this reaction to proceed according to the scheme

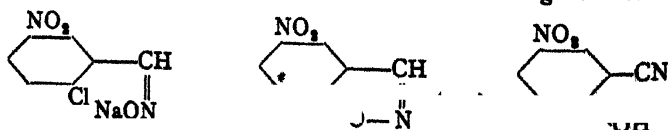


The monoxime actually formed, however, melts at 113° and is the one which had previously been assigned the alternative structure.

Meisenheimer pointed out that the oxidative disruption of triphenylisoxazole could be brought into agreement with the results of the Beckmann change if it is assumed that in the latter an exchange occurs between the OH group and the radical in the *anti*-position.



A similar reversal of Hantzsch's interpretation of the mechanism by which nitriles are formed is indicated by the work of Bishop and Brady on the conversion of aromatic aldoximes into isoxazole derivatives. One of the two 5-nitro-2-chloro-benzaldoximes undergoes this change

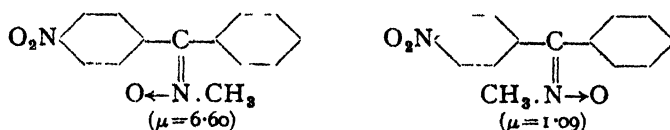


readily in the form of its sodium salt, the unstable benzo-isoxazole first produced being converted into the nitrile of 5-nitro-salicylic acid,

¹ For an account of these reactions see A. H. Blatt, *Chem. Rev.*, 1912, 22, 216.

and thus indicating the configuration given above. This isomeride, however, was originally assigned the reverse structure owing to the ease with which the acetyl derivative yields a nitrile.

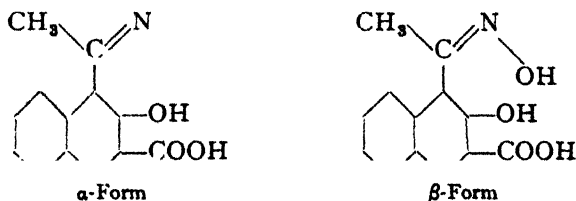
Additional support for the modern point of view has subsequently been gained by the use of independent methods. A determination of the dipole moments (p. 70) of the N-methyl ethers of the two *p*-nitrobenzophenone oximes¹ shows that one has $\mu = 6.60$ and the other $\mu = 1.09$. Since the only strong dipoles present are those of the groups NO_2 and NO , it follows that in the former compound these dipoles must be in a position to reinforce one another, and that in the less polar form they are oriented in opposite directions. The configurations are therefore represented as follows, and are found to be in agreement with



the structures deduced from the Beckmann transformation of the oximes, using Meisenheimer's interpretation of the reaction.

Another interesting case is that of the oximes of 2-hydroxy-1-acetyl-3-naphthoic acid.² One of these, the β -form, was obtained in the optically

OH



active state as its cinchonine and coniine salts, although on removal of the alkaloids racemisation rapidly ensued. The existence of an active form is explained by the "restricted rotation" (see p. 38) of the group attached to position 1 of the naphthalene nucleus, and the β -form is therefore given the structure indicated. No optical isomerism is exhibited by the α -form, in which it must be assumed that this group is free to rotate around the bond joining it to the aromatic radical. Beckmann transformations carried out with the α - and β -oximes are in agreement with these configurations, yielding compounds in which $\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$ and $\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_3$, respectively, are linked to position 1.

A suggestion which gives some insight into the mechanism of the Beckmann rearrangement was advanced by Mills.³ The driving force of the reaction is considered to be the superior affinity of oxygen for the central carbon atom, which leads to the replacement of the weak $\text{O}-\text{N}$

¹ L. E. Sutton and T. W. J. Taylor. *J.*, 1931, 2190.
Ann., 1932, 495, 249.

² Meisenheimer and co-workers.
³ W. H. Mills, *Presidential Address to British Association (Chemistry Section)*, 1932.

link by the stronger one joining oxygen to carbon. Under these conditions the first step in the reaction must be the movement of oxygen to carbon, thus displacing the nitrogen atom in a direction away from oxygen and in a sense corresponding to a *trans*-migration of the radicals attached to carbon.



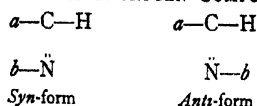
(d) *Geometrical Isomerism in Compounds containing the Group $-N=N-$*

According to Hantzsch the diazo-compounds also exist in stereoisomeric forms, the configurations of which are analogous to those of the ethylene derivatives. The experimental ground for this statement will be dealt with later (see p. 481) but the analogy in question may be illustrated by the following formulæ.

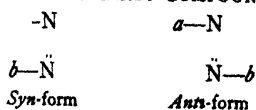
I. ETHYLENE COMPOUNDS



II. CARBON-NITROGEN COMPOUNDS



III. DIAZO-COMPOUNDS



The similarity of configuration can also be shown by use of the tetrahedron models, assuming as before that the valencies of trivalent nitrogen may under certain conditions be directed towards the three corners of a tetrahedron, at whose fourth lies the nitrogen atom itself. From this

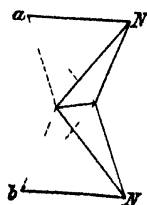


FIG 12

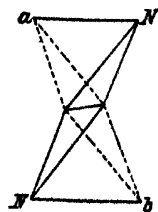


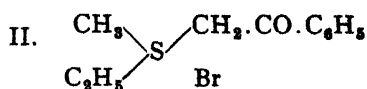
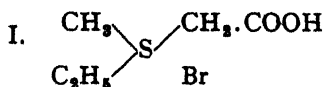
FIG 13.

point of view the diazo-compounds appear as double tetrahedra with one edge in common, as in Figs. 12 and 13.

3. Stereochemistry of Sulphur Compounds

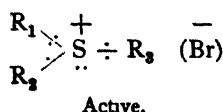
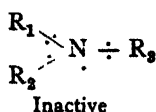
The success of Pope and Peachey in resolving a substituted ammonium salt gave a great impetus to the investigation of compounds containing

asymmetric atoms other than carbon. *Optically active sulphur compounds* were obtained almost simultaneously by Pope and Peachey and by Smiles. The former resolved methyl ethyl thietine bromide (I) by bringing it into reaction with silver (+)-camphor-sulphonate and repeatedly recrystallising the resulting methyl ethyl thietine (+)-camphor-sulphonates from a mixture of alcohol and ether. The camphor-sulphonic group was



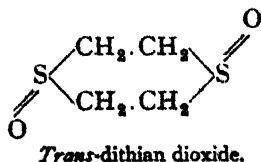
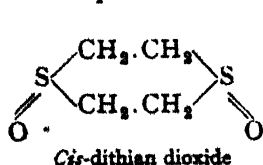
then exchanged for platinic chloride, yielding an active double compound containing PtCl_4 . Smiles resolved the methyl ethyl sulphide addition compound of ω -bromo-acetophenone (II) in a similar manner using (+)-camphor-sulphonic acid.

The optical activity of these compounds is not destroyed by the ionisation of bromine in aqueous or alcoholic solutions, and is therefore associated with the trisubstituted sulphonium ion. It is noteworthy that no activity has been found in the corresponding trivalent nitrogen



derivatives $\text{NR}_1\text{R}_2\text{R}_3$ despite the apparently identical arrangement of valency electrons around the two central atoms.

An interesting extension of our knowledge of the stereochemistry of sulphur was made some years later. It was found that sulphinic esters of the type, $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}\cdot\text{OC}_2\text{H}_5$, may exist in the optically active state, a discovery which was followed up by the resolution of *m*-carboxyphenyl methyl sulfoxide $\text{HOOC}\cdot\text{C}_6\text{H}_4\cdot\text{SO}\cdot\text{CH}_3$ and 4'-amino-4-methyl-diphenyl sulfoxide¹ $\text{H}_2\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{SO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$. A carbon atom linked to oxygen by a double bond is regarded as having a plane of symmetry bisecting both atoms and the double bond, but no such symmetry can be present in the sulfoxide linking, since sulfoxides exist in mirror-image forms. Oxygen in these compounds is evidently disposed above or below the plane occupied by the group C—S—C , a conjecture which is supported by the isolation of dithian dioxide in (inactive) *geometrically isomeric forms*,² the oxygen atoms being arranged in the *cis*- or *trans*-positions with respect to each other.



¹ Phillips, *J.*, 1925, 227, 2552; Harrison, Kenyon and Phillips, *J.*, 1926, 2079. ² E. V. Bell and G. M. Bennett, *J.*, 1927, 1798. For other compounds of similar type see E. V. Bell and G. M. Bennett, *J.*, 1928, 86; 1929, 15. F. G. Mann and Sir W. J. Pope, *J.*, 1922, 1052.

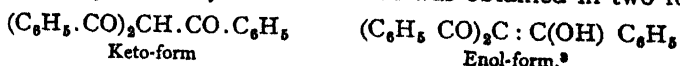
For optically active compounds of **silicon, germanium, tin, seleniur** etc., see K. Ziegler in Freudenberg's *Stereochemie*, p. 1168, and P. Pfeiffe *ibid.*, p. 1200.

TAUTOMERISM¹

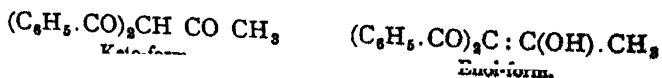
It is frequently found in organic chemistry that a substance behaves as though it possessed two or more structural formulæ. Such compounds are said to be *tautomeric* and the phenomenon is known as *tautomerism*. Familiar examples of this are hydrocyanic acid, which may react as hydrogen cyanide, $\text{H}\cdot\text{C}:\text{N}$ or as carbimide $\text{C}:\text{N}\cdot\text{H}$, and cyanic acid, for which we have the possible formulæ $\text{O}:\text{C}:\text{NH}$ and $\text{HO}\cdot\text{C}:\text{N}$.

The meaning of the word tautomerism has undergone considerable change since it was first introduced by Laar, and it is now clearly defined as follows²: "The term tautomerism is applied to the property exhibited by certain compounds of behaving in different reactions as if they possessed two or more different constitutions; that is, as if the atoms of the same compound or group were arranged in two or more different ways, expressible by different structural formulæ."

It is now known that tautomerism is due to the existence of two or more labile forms in equilibrium with each other, the isomerism in the majority of cases being caused by a transfer of a hydrogen atom from a carbon atom to another atom (oxygen or nitrogen) in close proximity, accompanied by the necessary rearrangement of single and double bonds. This picture of tautomerism as a dynamic equilibrium of isomeric compounds has been proved by the isolation in a number of cases of the two tautomeric forms. One of the earliest examples of this was provided by tribenzoylmethane which was obtained in two forms:



The classic example of keto-enol isomerism is acetoacetic ester (p. 277), both forms of which were first isolated by Knorr. It may therefore be taken as conclusively proved that in solution or the liquid state tautomeric compounds such as acetoacetic ester are mixtures of isomers or tautomers, which are capable of separate existence but have a great tendency to isomerise under the influence of heat, catalysts, etc. A case in which the isomers are solids is provided by *dibenzoylacetone*, $(\text{C}_6\text{H}_5\cdot\text{CO})_2\text{CH}\cdot\text{CO}\cdot\text{CH}_3$. The enolic and ketonic forms are comparatively easily isolated, the enolic form (m.p. 80-85°) being obtained by precipitation from alkaline solution by the addition of acetic acid and the ketonic form (m.p. 150-151°) from aqueous alcohol on slow evaporation.

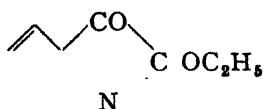


¹ *Tautomerism*, J. W. Baker (Routledge, 1934). ² "Oxford Definition," see T. M. Lowry, *Chem. Rev.*, 1927, 4, 231. ³ The term *enol* is derived from *en* denoting the double bond and *ol* representing the alcoholic hydroxyl group.

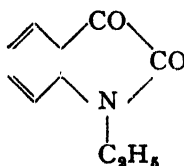
Tautomerism, then, is a type of isomerism in which the isomers are interconvertible; in liquid form or in solution the isomers are in dynamic equilibrium.

Tautomerism frequently arises from the migration of protons and is then termed *prototropy*. Many of the examples of tautomerism given in the sequel come under this heading.

It frequently happens that the amount of one of the forms in the equilibrium mixture is so small as to be negligible. In such cases only the stable form can be isolated, the labile form being no longer traceable by analytical methods: both forms may be detected by the formation of two types of derivatives. Isatin, for instance, has been isolated in one form only, but two ethyl derivatives, N-ethyl- and O-ethylisatin, are known.



O-Ethylisatin



N-Ethylisatin.

Simple ketones in solution react in the keto-form, but there is probably some of the enolic-form present to a very slight extent. On the other hand, phenols generally behave as enolic compounds, but on occasion as keto-compounds: *e.g.* naphthols in the Bucherer reaction (p. 581), phloroglucinol, etc. All these compounds according to our definition are tautomeric compounds, the only difference between them being the stability of the tautomeric forms.

The ratio of keto to enol in solution varies with temperature, solvent, etc.

For further examples of tautomerism see acetoacetic ester (p. 277), and pyrazole derivatives (see index).

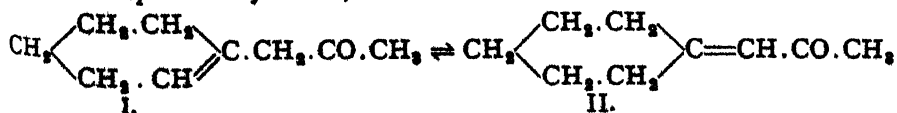
Another type of tautomerism, termed the Three-Carbon System, calls for comment. In the following paragraphs an arrow indicates the alternative position to which the hydrogen atom may travel.



The Three-carbon System, C=C—CH. The possibility of tautomerism of this kind is indicated by the transformation of $\beta\gamma$ -pentenic acid into the $\alpha\beta$ -acid on being boiled with alkali (Fittig), see p. 216. In this case both forms are usually stable and readily isolated. A more



mobile isomerism has, however, been shown to occur in the following ketonic compounds by Birch, Kon and Norris.¹



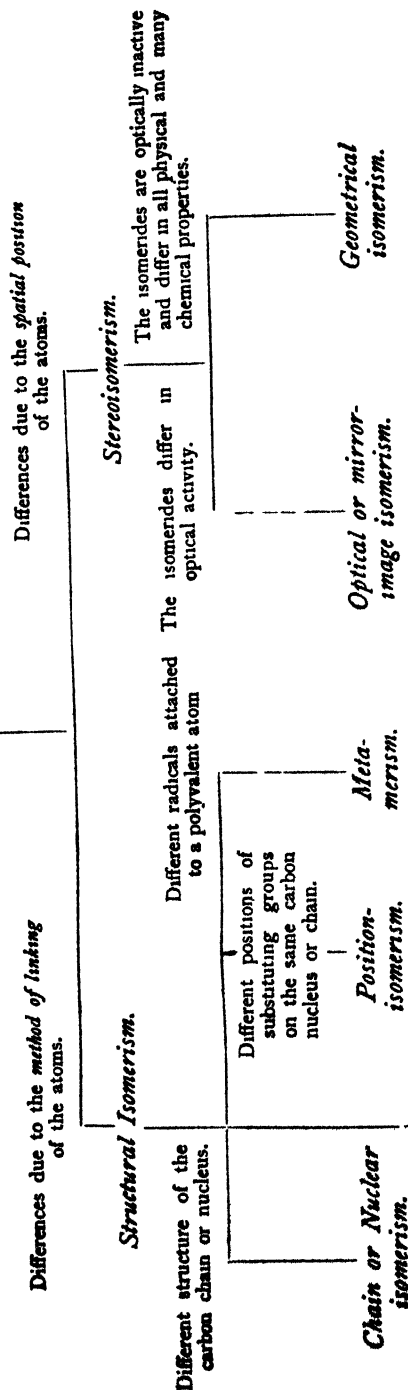
¹ *J.*, 1923, 123, 1361.

Polymerism.

Compounds have the same percentage composition (*i.e.*, same empirical formula), but have different molecular weights and different properties.

Isomerism.

Compounds have the same percentage composition and same molecular weight (*i.e.*, same molecular formula), but have different properties.

Isomerism.

The isomerides differ only by the position of a hydrogen atom in the molecule, and are characterised by a tendency to undergo mutual isomerisation :

Tautomerism or Dynamic isomerism.

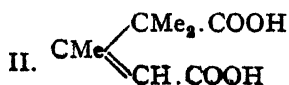
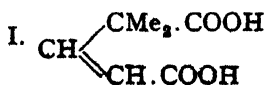
These form an equilibrium mixture containing a very large proportion of I.

Glutaconic Acids.—Under the heading of triads are included

glutaconic acid, $\text{HOOC} \cdot \text{CH}_2 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$, and its derivatives which were extensively investigated by Thorpe and his co-workers. Compounds of this type which contain mobile hydrogen furnish interesting examples of three carbon tautomerism accompanied by geometrical isomerism. In the case of the unsubstituted acid, the migration of a hydrogen atom leaves the molecular structure unchanged, although as was pointed out by Packer and Thorpe, the movement may or may not be accompanied by some interconversion of the *cis*- and *trans*-configurations, depending upon the spatial arrangement of the CH_2COOH group at the moment of transfer.

The arrangement of the constituent atoms in space is assumed to be governed by the tendency for similar groups to take up positions as remote as possible from one another. Such a tendency in the above acids can be satisfied owing to the power of free rotation about the single bond. It would thus be expected that the tautomeric change in the case of *trans*-glutaconic acid would take place mainly without alteration in the stereochemical configuration but that the *cis*-acid would be largely converted into the *trans*-form.

In compounds such as *aa*-dimethyl-glutaconic acid (I) and *aaβ*-trimethyl-glutaconic acid (II), the last mobile hydrogen atom has been

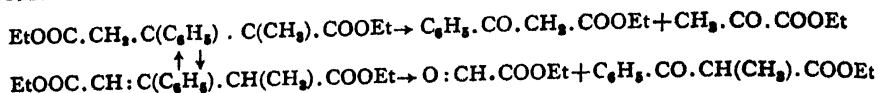


replaced by an alkyl group. These acids only exist in the usual *cis*- and *trans*-isomerides, of which the former alone yield anhydrides. Ordinary glutaconic acid, although of the *trans* type, also yields an anhydride. The latter, however, presumably corresponds to the *cis*-acid, as on treatment with cold water it is converted into the very unstable *cis*-glutaconic acid.¹ Anhydride formation is here due to the mobility of the glutaconic structure and is apparently preceded by isomerisation into the *cis*-acid.

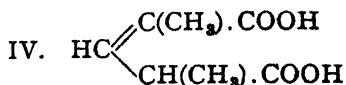
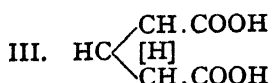
Tautomerism plays a more definite part in the case of alkyl substituted acids containing mobile hydrogen. Although many of these also exist in two modifications, the isomerism is not that of the ordinary geometrical type. Thorpe and Thole therefore suggested that the compounds are mobile tautomeric substances in which the α - and γ -carbon atoms function equally. Support for this view is given by the work of Feist,² who found that the ozonides of unsymmetrically substituted esters of glutaconic acid decomposed to give *four* products, two corresponding to each of the two possible positions of the double bond, instead of yielding the *two* products to be expected from a static compound with the double bond

¹ Malachowski, *Ber.*, 1929, 62, 1323. ² Feist, *Ann.*, 1922, 428, 25-75.

in a fixed position. The changes may be illustrated by the case of β -phenyl- α -methyl-glutaconic ester which on ozonolysis gave a mixture of the esters of benzoyl-acetic, pyruvic, glyoxylic and α -benzoyl-propionic acids.



Hence there is a symmetry about the molecule of glutaconic acid which is not conveyed in the usual formula with a fixed double bond. The earlier suggestion that the stable acids were represented by symmetrical formulæ, such as III ("normal" form), has now been



negated by the resolution of $\alpha\gamma$ -dimethyl glutaconic acid (IV) into optically active components.¹ Such a resolution could not have been effected had the molecular structure been of the symmetrical "normal" type, although it is possible that the latter form may exist as an ephemeral intermediate phase.

PHYSICAL PROPERTIES OF ORGANIC COMPOUNDS

In respect of physical properties there is no general difference to be traced between carbon compounds and those of other elements.

In modern times the investigation of physical properties has become of great importance in the study of organic compounds, being of value not only for the purpose of identification but also as a means of attacking the problem of molecular constitution.

1. Colour

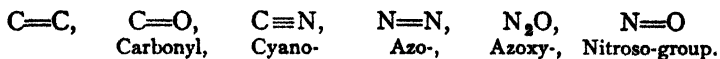
Among those properties which make their appeal directly to the senses that of colour stands out prominently. Some organic compounds possess colour and others are colourless. A careful distinction, however, must be drawn between colour and the ability to function as a dye. A compound may be strongly coloured and yet have no power, even with the aid of a mordant, to fix itself on the fibres of cotton, wool or silk.

Despite much experimental investigation from various quarters, the problem of the relation between colour and constitution is still unsolved. One of the main difficulties lies in the complexity of all the contributory factors. So far, no clear insight has even been obtained into the purely physical processes on which the phenomenon of colour depends, although it is known that the appearance of colour in a compound is connected

¹ T. H. McCombs, J. Packer and J. F. Thorpe, *J.*, 1932, 547.

with its power of absorbing rays of certain wavelengths. For a proper understanding of the relationship between colour and constitution we also require to know more about the inner structure and state of vibration of the molecule. At present all that can be said is that a number of regularities have been discovered bearing upon this point.

It appears from numerous researches that double bonds of practically any kind are the primary cause of colour. Apart from their mere presence, the position they occupy within the molecule also plays an important rôle. Following a suggestion of Witt,¹ the term **chromophore** has been applied to all those groups which give rise to colour when allied in suitable manner and sufficient number with hydrocarbon radicals. In general, however, the full development of colour is not attained in combination with hydrocarbon radicals alone, but only when the influence of the chromophore is strengthened by the presence of certain other groups, which Witt calls **auxochromes**. The most important chromophores are the groups :



Among coloured hydrocarbons may be mentioned fulvene, which contains three of the groups $C=C$. The presence of one or even of two such groups does not result in the production of any colour. Another comparatively weak chromophore is the carbonyl group. Colour is first noticeable in the presence of two of these, and then only if they are in very close proximity to one another. Thus diacetyl, $CH_3.CO.CO.CH_3$, with two carbonyl groups adjacent to one another, is a yellow liquid. The azo-group, on the other hand, is one of the strongest chromophores, even so simple a compound as diazomethane, CH_2N_2 , being yellow; whilst azobenzene, $C_6H_5-N=N-C_6H_5$, forms orange-red crystals. Another strong chromophore is the nitroso-group, the true nitroso-compounds being coloured an intense blue or green in the liquid state or in solution.

The auxochromes, the most important of which are the amino group (NH_2) and the hydroxyl group (OH), may act in two ways. On the one hand they may, by their presence, endow a substance with the capacity for salt-formation, with the possible production of a dye-stuff; and on the other, their introduction may lead to a deepening and intensification of the original colour. Those compounds containing a chromophore group, in which the entrance of an auxochrome produces a more strongly coloured substance or dye-stuff, were termed *chromogenes* by Witt.

It will be noticed over and over again in connection with the discussion of coloured substances and dye-stuffs that there is a strong tendency to associate colour with the presence of double bonds and in particular of a quinonoid structure in the molecule. Such unsaturated systems are undoubtedly resonating systems, and an interesting correlation of colour and mesomerism has been made (see p. 80).

¹ Witt, *Ber.*, 1876, 9, 522.

That the colour of solid matter varies continuously with the temperature has frequently been observed with organic compounds. The backward and forward continuity of the colour alteration is a special characteristic of this kind of reversible change. Stobbe, by whom this phenomenon was examined in the case of the fulgides,¹ described such compounds as *thermochromatic*.

2. State of Aggregation of Organic Compounds, Crystallisation

Comparatively few organic compounds are gaseous at the ordinary temperature, the majority of them exist normally in the liquid or solid state. In the latter case they may be amorphous or crystalline. Of these, the amorphous substances approximate more closely to liquids in their molecular condition, and their manipulation in the laboratory offers much greater difficulty than that of crystalline compounds. The crystalline form of an organic compound is often an important criterion of its identity.

Crystallisation is also employed for separating the individual constituents of a mixture from one another (*fractional crystallisation*). In some cases the organic substance may separate in the form of an addition compound with the solvent.

Many carbon compounds have the property of crystallising in two or more distinct forms, phenomena known as *dimorphism* or *polymorphism* respectively. Good examples of polymorphism are found in the *cis*- and *trans*-cinnamic acids.

Comparatively little is yet known as to the relation between chemical constitution and the crystal form of organic compounds. It has been established, however, that a definite connection exists between symmetry and asymmetry in molecule and crystal, and that changes in the chemical structure of the molecule also affect the conformation of the crystal. Asymmetry has already been discussed in dealing with the stereoisomerism of asymmetric carbon compounds (p. 26). The two stereoisomerides may differ in their configurations in such a way that they appear as enantiomorphous mirror-images of one another. Corresponding to this we often find a similar enantiomorphous difference in their crystal forms.

3. Melting-point

Under the influence of heat, solid compounds generally change their state of aggregation and become fluid. In many cases, however, chemical change takes place, followed by decomposition. Those substances that are fusible without decomposition possess a definite melting-point. At this point the solid and liquid forms of a body are in equilibrium with one another; the melting-point therefore coincides with the freezing-point.

The melting-point is one of the most important physical constants

¹ Stobbe, *Ann.*, 1911, 380, 17.

of an organic compound. In the vast majority of cases it is used for the identification of a substance and gives, in addition, valuable information as to the state of purity. While small impurities often bring about a considerable depression of the melting-point, larger amounts cause irregular and protracted melting, so that it is no longer possible to determine the point with certainty. Phenanthraquinone, for example, melts at 206° , 2-chloro-phenanthraquinone at 236° , but a mixture of the two in equal portions melts indefinitely between 160° and 190° .

Melting-points are quickly determined in a gas-heated apparatus, but an *electrically heated apparatus*¹ is now in use in which a minute quantity of material is observed on the stage of a microscope. This is especially convenient for compounds melting above 200° , or which are only available in small amount. This method is being widely used.

A knowledge of the *melting-points of mixtures* (mixed melting-points) is of special interest to the practical worker. At a certain composition the melting-point of a mixture of two substances reaches a minimum which lies below the melting-point of either of the two constituents. Two substances are therefore identical when a mixture of the two in any proportions has the same melting-point as either of the pure substances. The melting-point and composition of a mixture of substances is changed by repeated recrystallisation, and hence the constancy of the melting-point under this treatment is strong proof of the homogeneity and purity of the starting material.

The melting-point of successive members of a homologous series rises gradually with increase of molecular weight, but this is often accompanied by a minor alteration of rise and fall throughout the series. Members with an uneven number of carbon atoms have frequently a lower melting-point than the preceding compound containing one carbon atom less.

Among structurally isomeric compounds, that which is most symmetrically built usually has the highest melting-point. Thus of the isomeric di-substituted derivatives of benzene, the para-compound melts higher than the ortho- or meta-compounds.

4. Boiling-point and Distillation

The boiling-point of a liquid possesses the same importance as the melting-point of a solid, and is of great utility in the recognition, separation and purification of those compounds which are volatile without decomposition.

In most cases the boiling-point is determined by the same process of distillation which serves for its purification and isolation.

Many substances which cannot be distilled under ordinary barometric pressure owing to decomposition may be safely distilled under diminished pressure. In this case the internal pressure must be quoted with the

boiling-point. Distillation under diminished pressure is a most valuable means for the isolation and purification of high-boiling compounds, and plays an important rôle in laboratory as well as in technical work.

A further form of distillation, frequently employed in the separation and purification of compounds sparingly soluble in water, is *distillation in steam*. Many such compounds, even those of high boiling-point or which cannot be distilled alone without decomposition, volatilise more or less easily when heated with water, or when steam is blown through the mixture. The boiling-point of a mixture of two liquids, which do not dissolve one another, is attained when the sum of their respective vapour pressures is equal to the external (atmospheric) pressure. When this is the case both liquids distil. Since water is generally by far the more volatile of the two, it follows that the other liquid distils at a temperature much below its normal boiling-point. Steam distillation, therefore, is merely a special case of distillation under diminished pressure.

In order to isolate the individual constituents from a mixture of volatile compounds we make use of *fractional distillation*. This serves as a means of separation when there is a sufficient difference between the respective boiling-points of the constituents. Only if the boiling-points of two liquids lie far apart is it possible to attain a comparatively complete separation in one distillation. In this case the lower boiling compound comes over first at an approximately constant temperature, which then rises rapidly to the boiling-point of the less volatile compound, this finally distilling over pure. Generally speaking, however, it is not possible to obtain even an approximate separation in this way by a single distillation, and the process must be repeated several times. The efficiency of the operation is greatly increased by making use of a device known as a fractionating head (as designed by Wurtz, Hempel, Young and others) which brings about a partial condensation of the escaping vapour, returning the liquid so formed to the distillation vessel. In technical work a similar principle is adopted in "fractionating columns" (and dephlegmators), such as are described later under the purification of alcohols and benzene hydrocarbons. Recently "molecular distillation" or short-path distillation has been increasingly employed. By this method many substances with low vapour pressures and molecular weights above 300 have been fractionated with amazing efficiency.

Kopp was the first to point out the relationship existing between the constitution and boiling-point of an organic compound, and although the laws derived by him have not proved generally applicable, they nevertheless gave rise to a number of other fruitful investigations on the subject.

In a *homologous series* the boiling-point usually rises from member to member with increase in molecular weight. In the case of the normal primary alcohols, for example, the boiling-point rises at first fairly regularly by 18° to 22° for each additional CH_2 in the molecule. This increase gradually diminishes as we pass up the series. With the mixed aromatic hydrocarbons, the entrance of a CH_3 group into the side chain produces

the same difference in boiling-point as with the homologues of the fatty series, *i.e.* about 18° to 22° ; the entrance of a CH_3 group into the benzene ring, however, raises the boiling-point about 30° .

Regularities may also be traced between the boiling-points of compounds which do not belong to the same homologous series but show a definite structural relationship to one another. Thus an organic acid is commonly found to boil about 40° higher than the corresponding primary alcohol, and about 45° higher than its ethyl ester.

The boiling-points of the corresponding normal hydrocarbons of the series $\text{C}_n\text{H}_{2n+2}$, C_nH_{2n} , and $\text{C}_n\text{H}_{2n-2}$ approximate closely to one another (*e.g.* $\text{C}_{18}\text{H}_{38}$, 181.5° , $\text{C}_{18}\text{H}_{36}$, 179° , $\text{C}_{18}\text{H}_{34}$, 184°).

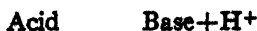
In the case of isomeric substances which differ in the construction of their carbon chains, the highest boiling-point corresponds to the normal structure in which no side chains are present. As soon as side chains appear the boiling-point is lowered, and the more branched the carbon chain the greater is the difference observed.

5. Solubility

Many carbon compounds are more or less readily soluble in water; for such as are not we may employ as solvents alcohol, ether, ligroin (light petroleum), glacial acetic acid or benzene, as well as mixtures of these liquids. A selected solvent is frequently utilised in the identification, isolation or purification of a compound. Hydrocarbons are either insoluble or very sparingly soluble in water, but if hydrogen in these compounds is replaced by oxygen or the hydroxyl group the solubility increases, and becomes the greater as more hydrogen is substituted. The first members of the homologous series of alcohols, aldehydes, ketones and acids are soluble in water, but as the proportion of carbon increases the solubility in water diminishes.

6. Acidity and Basicity

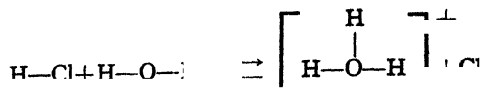
The terms acids and base are among the most important in the chemist's vocabulary and have been defined in various ways.¹ Probably the definition which finds most acceptance with organic chemists is that advanced independently by Bronsted and Lowry, according to which an acid is a substance capable of yielding a proton and a base one which is capable of accepting a proton.



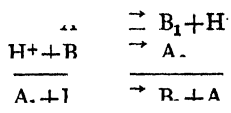
This equation, however, ignores the part played by the solvent, a part frequently important. For instance, hydrogen chloride is a non-conductor until it is dissolved in water. This is most simply explained by assigning

¹ See R. P. Bell, The Use of the Terms "Acid" and "Base", *Quart. Rev.*, 1947, 1, 113.
A. Albert, *Chem. and Ind.*, 1947, 25, 51.

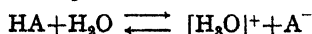
a basic role to water, which because of its lone electron pairs (represented by dashes in the following equation) can unite with a proton to give an *oxonium ion*.



It will be noted from this equation that not only the reactants but also the products form an acid-base pair, for the oxonium ion can obviously lose a proton and is therefore by definition an acid, while the chloride ion can unite with a proton to form hydrochloric acid and is therefore a base. A more general equation to represent acid-base reactions is given by the following equation in which B_1 is the *conjugate* (*i.e.* corresponding) *base* of the acid A_1 and A_2 is the conjugate acid of the base B_2 .



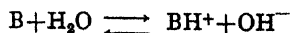
The strength of an acid is measured by means of the *acidity constant* K_a which follows from the equation :



Hence (the quantity of water being assumed to be constant)

$$K_a = \frac{[H_3O]^+[A^-]}{[HA]}$$

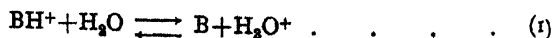
The strength of a base, K_b , is derived from the equation,



and hence

$$K_b = \frac{[BH^+][OH^-]}{[B]}$$

The general acceptance of the Bronsted-Lowry definition has resulted in the strengths of bases being measured not by their K_b values, but by the acid constant K_a of the conjugate acid BH^+ . This functions as an acid according to equation 1, and the value of the acid constant must be given by equation 2.



$$K_a = \frac{[H_3O]^+[B]}{[BH^+]} \quad (2)$$

The two constants of a base in a given solvent are dependent on one another since

$$K_a = \frac{[H_3O]^+[OH^-]}{K_b} = 10^{-14}$$

It is obvious that the stronger a base the greater is its K_b value and the smaller its K_a value

It is now customary to replace the constants by the logarithmic functions pK_a and pK_b , which are defined by the equations :

$$pK_a = -\log K_a \quad pK_b = -\log K_b$$

This leads to more workable figures. For instance, if

$$K_a = 10^{-6}, pK_a = 6.$$

On account of the minus sign in the equations it should be observed that the pK_a values of bases increase with increasing basicity. pK_a values of acids, on the other hand, decrease with increasing strength. In general terms it may be stated that very strong bases have pK_a values above 10 : moderately strong bases lie between 7 and 10 : weak bases 4-7 ; and very weak bases below 4. Acids, on the other hand, with pK_a values greater than 7 scarcely redden litmus.

pK_a Values

Acids			Bases		
Hydrochloric acid	.	*	Sodium hydroxide	.	*
Oxalic acid	.	2	Guanidine	.	*
Benzoic acid	.	4.2	Methylamine	.	10.7
Acetic acid	.	4.8	Ammonia	.	9.2
Hydrocyanic acid	.	9.0	Aniline	.	4.6

* Too strong acid or base to be measured.

Strength of Acids and Bases. Influence of Substitution on the Dissociation of Acids.—The conductivity has been found to give a measure of the strengths of acids and bases in so far that the stronger acid or base is the better conductor. On these grounds Arrhenius in 1884 suggested that the strength of an acid was proportional to its conductivity, or rather to its degree of dissociation. A corresponding relationship also holds for bases.

It has long been known that the strength of an acid such as acetic acid is increased when a hydrogen atom is replaced by chlorine. Thus monochloroacetic acid, $\text{CH}_2\text{Cl}.\text{COOH}$, is distinctly stronger than acetic acid, $\text{CH}_3.\text{COOH}$; dichloroacetic acid, $\text{CHCl}_2.\text{COOH}$, is stronger still ; and trichloroacetic acid, $\text{CCl}_3.\text{COOH}$, even more so. The same sequence is to be observed in the dissociation constants K

$$\begin{array}{cccc} \text{CH}_3.\text{COOH} & \text{CH}_2\text{Cl}.\text{COOH} & \text{CHCl}_2.\text{COOH} & \text{CCl}_3.\text{COOH} \\ 1.82 \times 10^{-5} & 155 \times 10^{-5} & 5,140 \times 10^{-5} & 121,000 \times 10^{-5} \end{array}$$

A similar increase in acidity occurs when hydrogen is replaced by many other substituents, although methyl and amino groups diminish the value. Different substituents affect the acid strength of acetic acid in the order $\text{NO}_2 > \text{CN} > \text{COOH} > \text{Cl} > \text{Br} > \text{I} > \text{OCH}_3 > \text{H} > \text{CH}_3$. In the case of benzoic acid substitution in the ortho position exerts a greater influence than in the meta or para position, and the above order of groups also holds approximately for the *o*-substituted acids. The fundamental

nature of the change following on substitution is shown by the fact that the same sequence of groups is often repeated in their relative effect on other properties. These *polar* regularities are sometimes of value in solving problems of constitution.

Hydrolysis.—In aqueous solution the salt of a weak acid or base undergoes a partial decomposition termed hydrolysis. A solution of aniline hydrochloride, for example, contains besides aniline hydrochloride a certain amount of free aniline and free acid, the latter of which is in addition subject to electrolytic dissociation. These constituents of the solution exist in a state of equilibrium which varies with temperature and concentration. In a similar manner a solution of sodium phenate contains a proportion of free phenol and sodium hydroxide. Water therefore possesses the property of partially liberating weak acids or bases from their salts. The amount of hydrolysis may be determined quantitatively by conductivity measurements and a variety of other methods.¹

In a somewhat different sense the term *hydrolysis* is employed to indicate the decomposition of esters, amides, nitriles, etc., through the agency of water (see pp. 75, 162, 228). Generally speaking, the reagents actually used in such cases are acids and alkalis which bring about the reaction with greater velocity and completeness.

7. Polar Properties of Organic Compounds

Within the last few years considerable progress has been made in our knowledge of the electrical structure of compounds, more especially with reference to the changes produced by substitution. It has long been usual to classify substituent groups as *electronegative* or *electropositive* in type, according to their influence upon the ionisation of acids and bases. Electronegative groups, in general, increase the dissociation constant of an organic acid, whilst electropositive groups lower the value. But it is only recently that the work of Debye, J. J. Thomson and others has enabled us to give a precise and quantitative meaning to the polarity of substituent groups. The present standpoint may be summarised briefly as follows.

The electrical centre or centre of gravity of the electrons in a molecule may or may not coincide with that of the protons. In the former case the molecule will be non-polar with respect to an external field, but in the latter case it will behave as an electrical doublet or dipole. If



FIG. 14.

we represent the molecule diagrammatically as in Fig. 14, the positive and negative centres (or poles) may be indicated by + and - respectively, separated from one another by a distance d . Obviously the molecules will have a definite turning moment in an electrical field and will tend to arrange themselves uniformly in such a manner as to produce a system of minimum potential energy, a tendency which will be opposed by the heat vibration of the molecules. The magnitude

¹ See Findlay, *Practical Physical Chemistry* (Longmans).

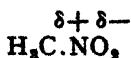
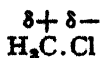
of the turning moment depends upon e the charge at the poles and d their distance apart. A quantitative measure of this function is given by the **dipole moment**, μ , which may be calculated by various methods from data referring to the refractivity and dielectric constant of the compound in the gaseous state or in dilute solution in a non-polar solvent such as benzene or hexane.¹ As a result of many investigations on these lines it has been found that hydrocarbons in general have an electrical moment which is either zero or of very small magnitude. Mono-substituted hydrocarbons, on the other hand, give values of μ which are characteristic of the particular substituent present and depend only in minor degree upon the nature of the hydrocarbon radical to which it is attached. This is illustrated by the figures for derivatives of ethane and benzene given in the table, in which the signs $+$ and $-$ are introduced solely for the purpose of indicating the electropositive or electronegative character of the polar substituent.

*Dipole Moments of Compounds**

μ	μ
$\text{C}_2\text{H}_5 \cdot \text{NH}_2$ $+1.31$	$\text{C}_6\text{H}_5 \cdot \text{NH}_2$ $+1.5$
$(\text{C}_6\text{H}_{14})$ 0	$\text{C}_6\text{H}_5 \cdot \text{CH}_3$ $+0.4$
$\text{C}_2\text{H}_5 \cdot \text{COOH}$ -0.6 (?)	C_6H_5 0
$\text{C}_2\text{H}_5 \cdot \text{O} \cdot \text{C}_2\text{H}_5$ -1.2	$\text{C}_6\text{H}_5 \cdot \text{COOH}$ -0.9 (?)
$\text{C}_2\text{H}_5 \cdot \text{OH}$ -1.7	$\text{C}_6\text{H}_5 \cdot \text{OCH}_3$ -1.2
$\text{C}_2\text{H}_5 \cdot \text{I}$ -1.7	$\text{C}_6\text{H}_5 \cdot \text{I}$ -1.25
$\text{C}_2\text{H}_5 \cdot \text{Br}$ -1.9	$\text{C}_6\text{H}_5 \cdot \text{Br}$ -1.5
$\text{C}_2\text{H}_5 \cdot \text{Cl}$ -2.0	$\text{C}_6\text{H}_5 \cdot \text{Cl}$ -1.5
$\text{C}_2\text{H}_5 \cdot \text{CHO}^*$ -2.7	$\text{C}_6\text{H}_5 \cdot \text{OH}$ -1.7
$\text{C}_2\text{H}_5 \cdot \text{CN}$ -3.3	$\text{C}_6\text{H}_5 \cdot \text{CHO}$ -2.8
$\text{C}_2\text{H}_5 \cdot \text{NO}_2$ -4.0	$\text{C}_6\text{H}_5 \cdot \text{CN}$ -3.85
	$\text{C}_6\text{H}_5 \cdot \text{NO}_2$ -3.9

* By analogy with CH_3CHO

It appears that in the majority of cases, at all events, the dipole is located within the substituent group or in the neighbourhood of the bond joining it to the adjacent carbon atom. Among electronegative groupings the positive end of the dipole is directed towards the parent hydrocarbon radical, the reverse arrangement holding for electropositive groups.

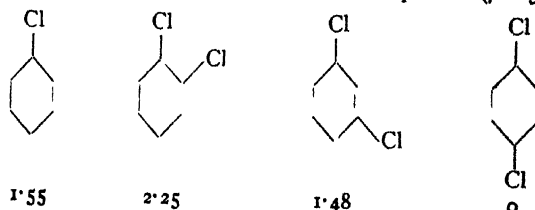


The orientation of the dipole for electronegative groups was deduced, for example, from the case of a compound $\text{R} \cdot \text{CH}_2\text{Cl}$, in which chlorine tends to separate as chloridion, Cl^- , taking with it *both* of the covalency electrons originally binding it to carbon. It is therefore assumed that

¹ The external field will also tend to distort the dipole to an extent depending on the strength of the field and the deformability of the molecule. For further details reference should be made to *Polar Molecules*, by P. Debye (Chemical Catalogue Co., New York, 1928); *Dipole Moments*, R. J. W. Le Fèvre, 1948. ² The majority of these values have been determined by J. W. Williams, C. P. Smyth and J. Højendahl, and are taken from Debye's *Polar Molecules* (Leipzig, 1929). Some of the figures are subject to minor corrections.

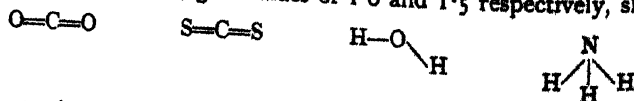
in the carbon-chlorine link, the covalency electrons are normally situated in closer proximity to chlorine than to carbon (*e.g.* C :Cl) thus leading to partial charges on carbon and chlorine as indicated. This is supported by the fact that the nitro group is written with the same orientation in order that its electronic structure may conform to the requirements of the octet theory (see p. 18). Dipoles of electropositive type must therefore have the opposite arrangement.

The value of μ for a monosubstituted hydrocarbon gives a measure of the electric moment, but affords no information regarding the sign or orientation of the dipole. In some cases the latter can be deduced, as has been shown above for the chloro and nitro groups. By using these groups as standards of reference, other substituents may then be classified as electronegative or electropositive by means of the vectorial method suggested by J. J. Thomson. *o*-Dichlorobenzene, for instance, has a much greater moment than chlorobenzene, because the two CCl-dipoles in this compound are arranged in such a manner as to reinforce one another. *p*-Dichlorobenzene, however, behaves in a uniform electrical field as a non-polar substance, giving $\mu = 0$. In this case the two CCl-dipoles are oriented in opposite directions and their effects cancel out. Similarly, Cl and NO₂ being both of the electronegative type, it is found that among the nitro-chlorobenzenes the *o*-compound ($\mu = 3.78$) gives a



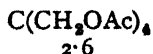
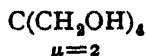
higher moment than the *m*- ($\mu = 3.18$) or *p*-compound ($\mu = 2.36$). Among the methyl aminobenzoates, however, where the two groups are of the opposite type, the moment is least ($\mu = 1.0$) in the *o*-compound, of intermediate value ($\mu = 2.4$) in the *m*- and highest ($\mu = 3.3$) in the *p*-compound in which the dipoles reinforce one another. Relationships of the same kind are found among *cis* and *trans* isomerides, *e.g.* of the types R.CH : CH.R and R.N : N.R, the *cis* forms having considerable dipole moments and the *trans* forms zero value (see azobenzene).

Molecules such as carbon tetrachloride, carbon disulphide and carbon dioxide also possess zero moment, from which it follows that they are symmetrical in structure, the last two being necessarily linear. Water and ammonia, however, give values of 1.6 and 1.5 respectively, showing

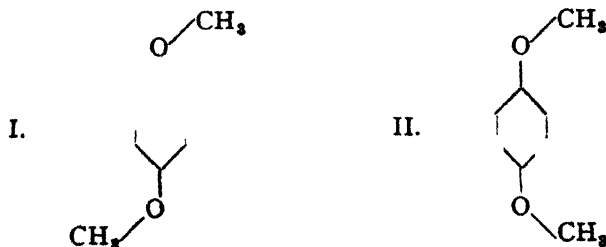


that water is not of linear type and that ammonia has a pyramidal and not a planar arrangement.

Many other apparently symmetrical compounds give finite values for μ , and in these cases the polarity has been found to arise from a non-linear arrangement of valency bonds such as occurs with divalent oxygen and trivalent nitrogen. Probably the molecules assume an unsymmetrical formation as a result of the forces of attraction or repulsion exerted by neighbouring groups on one another, or merely owing to the free rotation of the unsymmetrical substituents around the bonds uniting them to the nucleus. Thus pentaerythritol, $C(CH_2OH)_4$, and certain of its derivatives containing oxygen have been shown to possess large moments, although the corresponding bromo derivative, $C(CH_2Br)_4$, has zero value.



The reason for this is best illustrated by reference to hydroquinone dimethyl ether. Since each methoxyl group may rotate freely about the bond joining oxygen to the carbon atom of the benzene ring, the molecule when not in the solid state must be regarded as existing in all possible forms between the two extremes I and II. Of these, structure I (*trans*) will have zero dipole moment, whereas II (*cis*) will have a moment of appreciable magnitude. Intermediate forms also possess finite moments,



which diminish in value as the structure approaches that of I. Hence by summation of the various forms the compound possesses a definite moment, which is due to the angle between the oxygen valency bonds. A similar example is given by *p*-phenylenediamine, $H_2N.C_6H_4.NH_2$, where the moment arises from the pyramidal distribution of the nitrogen bonds.

In the following section it will be shown how information gained from the study of dipole moments has been used to explain the changes in the physical and chemical properties of compounds arising from the substitution of hydrogen by other atoms and groups.

Influence of Dipoles on the Properties of Compounds

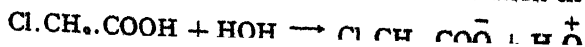
Evidence now available shows that many properties of compounds are directly influenced by the sign and magnitude of the dipoles present in the molecule. Effects of this kind have been investigated more especially in connection with the dissociation of acids, the velocity of chemical reactions, and molecular association.

One general cause of molecular association in polar compounds is the orientation of dipoles in such a manner that the positive end of one is linked to the negative end of another, and *vice versa*, to form a close system similar to that obtained by placing two bar magnets side by side with north and south poles together. An arrangement of this kind is termed **dipole-association**; other and more complex formations of dipoles may also occur. The orientation of the polar group is only loose and temporary, usually breaking down under the heat vibration of the molecules. Nevertheless it is responsible for the well-known phenomena of association, including elevation of boiling point. In determining the value of the dipole moment this disturbing influence must be eliminated as far as possible by using data for the compounds either in a state of vapour or highly diluted by a non-polar solvent such as benzene. Under these conditions the polar molecules are so far removed from one another that little mutual interaction takes place.

Another general influence arising from the presence of a polar group is the **inductive effect**. When a polar substituent is attached to a chain of carbon atoms, induced charges of a sign similar to that of the dipole introduced are relayed throughout the molecule. The effect is believed to operate partly through the chain and partly through space, but as we are not yet able to differentiate between these two processes they are included together in the term inductive effect. The origin of the change lies in the attraction or repulsion of the covalency electrons in the chain due to the greater influence exerted by the nearer end of the dipole.

Thus in the chain $\text{Cl}^-\leftarrow\overset{+}{\text{CH}_2}\leftarrow\text{CH}_2\leftarrow\text{CH}_2\leftarrow$, the nearer positive pole of the CCl-dipole attracts and displaces the electrons in the direction shown by the arrows (*electron shift*). Between any pair of adjacent carbon atoms the covalency electrons are therefore situated nearer the left hand than the right hand atom and an induced dipole of the type $\text{CH}_2^--\overset{+}{\text{CH}}$ is set up. The induced effect diminishes rapidly as the distance from the original dipole increases but in suitable cases it can be traced as far as the third or even fourth carbon atom, after which it becomes too small for detection.

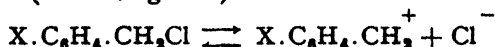
The induced effect provides an explanation for the observed rise in the **dissociation constant** of an aliphatic acid which follows the introduction of an electronegative substituent. In chloroacetic acid, for example, the electron shift due to the CCl-dipole makes it easier for the electron pair binding the ionisable hydrogen atom to oxygen to pass under sole control of the latter atom, thus displacing the equilibrium in the following expression to the right and increasing the degree of dissociation in comparison



with acetic acid. In a base, a dipole of electronegative type diminishes the basicity.

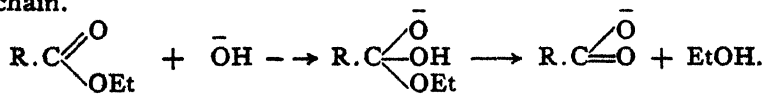
With electropositive groups the inductive effects are in the opposite direction to those indicated above, *e.g.* $\overset{+}{\text{X}} \rightarrow \text{CH}_2 \rightarrow \text{CH}_2 \rightarrow \text{CH}_2 \rightarrow$. Thus a methyl group tends to reduce the strength of an acid and to increase that of a base. Ingold describes the inductive effect of the electronegative group in $\text{X} \leftarrow \text{C}$ as $-I$, and that of the electropositive group in $\text{X} \rightarrow \text{C}$ as $+I$. The relative effects of some of the commoner substituents on dipole moments and the dissociation constants of aliphatic acids are given by $\text{NO}_2 > \text{halogens} > \text{H} > \text{CH}_3$.

Olivier showed that the reverse sequence, $\text{CH}_3 > \text{H} > \text{halogens} > \text{NO}_2$, holds for the velocity of hydrolysis of substituted benzyl chlorides in aqueous alcohol, $\text{X} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2\text{Cl} + \text{HOH} \longrightarrow \text{X} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2\text{OH} + \text{HCl}$. Under the conditions employed the rate of hydrolysis depends chiefly on the speed of ionisation of the halide, a process which is facilitated by electron-repulsive (electropositive) groups and retarded by those of electron-attractive (electronegative) character.



A similar diminishing sequence is found for the velocities of reaction of a number of chemical processes, including other hydrolyses in acid media, all of which are listed together¹ as belonging to "type A."

On the other hand the sequence, $\text{NO}_2 > \text{halogens} > \text{H} > \text{CH}_3$, holds for various other reactions which are classed as "type B." An example of this kind is given by the **alkaline hydrolysis of esters**, such as those of substituted benzoic, phenylacetic and cinnamic acids.² Here the effective agent in the reaction, the hydroxyl group, has its full complement of electrons and is therefore a **nucleophilic reagent**, seeking a point of attack (the positive end of the CO-dipole) at which there is a deficiency of electrons. For this reason the reaction is assisted by the presence of groups such as NO_2 which tend to withdraw electrons from the carboxylic side chain.



The **alkaline hydrolysis of benzyl chlorides** falls into the same category.³

As will be seen later, the inductive effect is also observed in **benzene substitution**, which usually involves an **electrophilic reagent**,⁴ *i.e.* one seeking a point of attack rich in electrons. Hence, in general, the reaction proceeds more rapidly when an electropositive group is already linked to the ring, since this tends to repel electrons into the benzene nucleus, but is retarded by the presence of an electronegative group which tends to withdraw electrons. A simple inductive influence, however, is only



¹ See Ingold and Rothstein, *J.*, 1928, 1217; Williams, *ibid.*, 1930, 40. ² Kindler, *Ann.*, 1926, 450, 1; 1927, 452, 90; 1928, 464, 278. Ingold and Nathan, *J.*, 1936, 222. ³ Shoosmith and Slater, *J.*, 1924, 223, 1312, 2278. ⁴ Electrophilic and nucleophilic reagents are also described as kationoid and anionoid respectively.

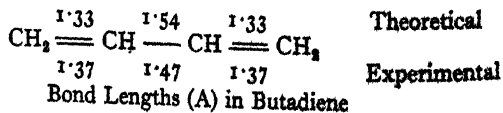
produced by a substituent in a saturated chain of atoms ; in a conjugated system of single and double bonds powerful effects of another character, known as *electromeric*, may be set up with substituents such as hydroxyl, which contain unshared electrons on the atom directly bound to the unsaturated system. These are discussed under benzene substitution, p. 438.

8. Bond Lengths

There can be little doubt that the application of physical methods in the investigation of organic compounds has introduced a precision and insight into molecular structure which would have been impossible by purely chemical means. A notable example of this is found in the use of spectroscopy, X-ray and electron diffraction to measure bond lengths and bond angles so that we now have geometrically exact models of many organic substances. The results show that, except in conjugated double bond systems, each type of bond has its own characteristic *bond length*. Expressed in a different way, the length of a bond is characteristic of the two atoms involved and of its *multiplicity* (i.e. whether it is single, double, or triple).¹ This is shown by the C—C bonds in diamond and the paraffins having a length of 1.54 Å and the C=C bonds in the olefins having a length 1.33 Å.² A few lengths of bonds frequently encountered in organic chemistry are given in the following table .

<i>Bond Lengths</i>			
(In Ångstrom Units 1 Å = 10 ⁻⁸ cm)			
C — C	1.54	C — O	1.42
C = C	1.33	C = O	1.20
C ≡ C	1.20	C ≡ O	1.13
		(Carbon monoxide)	
C — N	1.47	N — O	1.36
C = N	1.30	N = O	1.15
C ≡ N	1.15		
C — H	1.09		

Bond lengths such as those given above together with a knowledge of bond angles, provide valuable aids in the studies of topics such as steric hindrance and diphenyl isomerism (p. 38). Furthermore, divergences from the characteristic bond lengths throw light on conjugation and resonance (see p. 77). Thus the inadequacy of the simple valency bond formula of butadiene is shown by the lengths of the single bond and the double bonds in the molecule which differ considerably from those listed above.



¹ C. K. Ingold, *Structure and Mechanism in Organic Chemistry* (Bell, 1953), p. 14.

² P. W. Allen and L. E. Sutton, *Acta Cryst.*, 1950, 3, 46.

Other examples of the use of bond lengths in determining the fine structure of organic compounds will be found later in the text.

9. Resonance or Mesomerism¹

In recent years information from a number of sources has necessitated a revision of certain organic formulæ. Reference has already been made to the case of the nitro group, originally formulated as I and later modified to II in order to bring it into agreement with electronic theory, since nitrogen in its higher valency state has only four covalent links, the fifth being electrovalent.

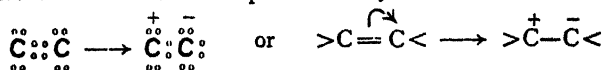


Formula II was found to be inadequate when the dipole moment of *p*-dinitrobenzene proved to be zero, thus showing that the structure is a symmetrical one. Had the nitro group contained a single co-ordinate link as in II, it would have been electrically unsymmetrical and *p*-dinitrobenzene would have resembled hydroquinone dimethyl ether and *p*-phenylene-diamine in having a moment of considerable magnitude (compare p. 73). Further confirmation of symmetry is given by the case of the closely related nitrate ion, in which X-ray and infra-red spectroscopic data show all three oxygen atoms to be in exactly the same electronic condition. According to present views, the nitro group is said to be in a **state of resonance or mesomerism**, with an actual electronic arrangement intermediate between those represented by the extremes II and III (which are known as **the unperturbed or contributing forms**) and possessing greater stability than either of these. This mesomeric structure is described as a **resonance hybrid** of forms II and III, but it must be emphasised that a definite intermediate arrangement of electrons is implied and that there is no suggestion of anything resembling an oscillation between the unperturbed forms. A consideration of formulæ II and III shows that in the case of the nitro group the intermediate mesomeric state must be a symmetrical arrangement, such as is conveniently expressed in IV, which conveys the idea of a negative charge distributed over both oxygen atoms.

In any given compound the various contributing or resonating structures may be derived from each other by **electromeric displacements**, i.e. by changes in which electrons, whilst remaining in one octet, enter or leave another. A simple example of electromeric displacement, which was first postulated by Lowry in 1923, is afforded by an ethylene derivative. A pair of electrons taking part in the double union may be supposed to be transferred bodily to one of the carbon atoms, giving it a negative charge and leaving the remaining carbon positively charged.

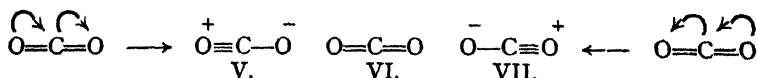
¹ See *Modern Theories of Organic Chemistry*, by H. B. Watson (Oxford, 1941); *Physical Organic Chemistry*, by L. P. Hammett (McGraw-Hill Book Co., 1940).

Transfers of this kind are represented by curved arrows indicating the



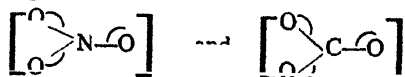
direction of the change, and are assumed to be *completed* only momentarily at the time of reaction, *e.g.* during the instant preceding addition to the double bond. Whether the displacement tends to be greater in one direction or in the reverse sense will depend on other factors, including the nature of the groups attached to the carbon atoms. Ethylene itself has a symmetrical structure and the mesomeric form approximates closely to the non-polar arrangement $\text{CH}_2 = \text{CH}_2$, which is intermediate between the two polar forms derived in the above manner.

Another simple illustration of resonance is given by carbon dioxide which may be written in the three contributing forms V, VI and VII



It will be seen that V and VII are derived from VI by electromeric displacements, a pair of electrons leaving the carbon octet and becoming attached to one oxygen atom, which therefore acquires a negative charge. Simultaneously the carbon octet is completed again by the movement of two unshared electrons from the oxygen at the other end of the molecule leaving this oxygen with a positive charge (oxonium state) and attached by a triple bond in place of the original double bond.

Infra-red and X-ray spectroscopic investigations on carbonates have established the fact that in the carbonate ion as in the nitrate ion the oxygen atoms are all in the same electronic condition. The ionic structures are therefore in a state of resonance and are represented by formulae such as the following



The conception of resonance or mesomerism in organic compounds was introduced by Ingold,¹ and the explanation of the stability of the mesomeric state is due to Pauling. The latter showed that resonance may be deduced from a wave-mechanical treatment, applicable to any molecule capable of being represented by two or more structures in which the positions of the nuclei are approximately the same and the energies are of the same order of magnitude, but in which the electrons have different arrangements.² It can then be proved mathematically that there is a state intermediate between those which are expressed by our usual formulae, and that this possesses a minimum of energy and hence a maximum stability. In general, therefore, this intermediate or mesomeric state will be the form in which the molecule exists.

A consequence of resonance, which is well illustrated in the case of

¹ *Chem. Rev.*, 1934, 15, 225.

² Cf. H. B. Watson. *Loc. cit.* p. 220.

carbon dioxide, is that linkages formerly represented as double bonds may assume a character intermediate between double and single bonds. In these cases the lengths of the interatomic distances are also found to be intermediate, and this has already been exemplified by the resonating butadiene molecule (p. 76). In benzene, which exhibits a considerable degree of resonance, the hybrid bonds are each found to be 1.39 Å. A similar modification of both single and double bond lengths is found in other conjugated systems. From such data it is often possible to estimate approximately to what extent double bond character in the resonating structures has been changed into single bond character in the resonance hybrid. Any modification of structure is accompanied by corresponding alterations in the chemical properties.

Pauling has pointed out that the actual heat of formation of a compound exhibiting resonance is more than the values calculated for the corresponding contributing forms from the heats of rupture of simple covalent links. Experimental support is thus provided for the mathematical deduction that the resonance hybrid has less energy than the contributing structures and is therefore less reactive. The difference between the actual energy and that calculated for the contributing forms is termed the **resonance energy**, which is of greatest magnitude in cases where these are equivalent structures. If one of the contributing forms is of much lower energy than the others, the mesomeric state will approximate more closely to this form; the remaining forms then only make an insignificant contribution to the resonance hybrid and the chemical behaviour of the compound will resemble that of the form making the greatest contribution.

Pauling has also shown that aromatic compounds such as benzene, naphthalene and pyridine possess considerable resonance energy, thus accounting for their stability. In the case of benzene the two contributing forms are VIII and IX, leading to the mesomeric form X, in which



VIII



IX



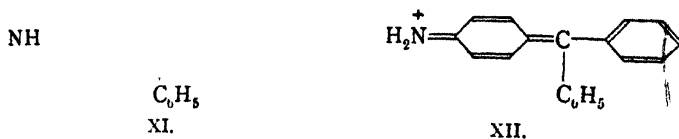
X

the double bond character is greatly diminished and therewith the reactivity towards additive and oxidising agents (p. 431). This rational explanation of aromatic character represents one of the triumphs of the theory of resonance. On the other hand pyrrole, with feeble aromatic properties, has only a small resonance energy. References will be found later in the text to resonance in derivatives of naphthalene, pyrazole and other compounds.

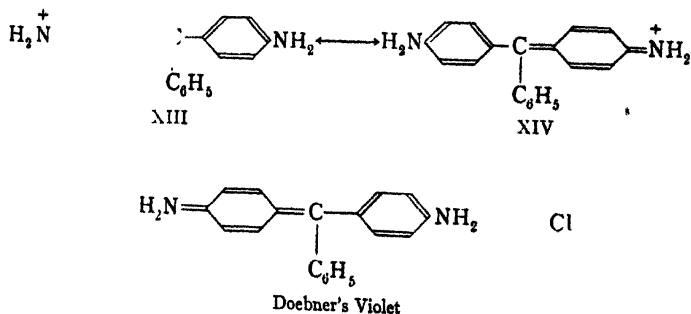
The theory has been successfully applied to the problem of colour and dyeing.

There can be little doubt that the intense colour of dyestuffs is closely

linked with the phenomenon of resonance. According to Bury,¹ one of the functions of an auxochrome is to introduce the possibility of resonance. On this theory, chromophores are coloured resonance hybrids with no dyeing properties; chromogens are dyestuffs owing to the presence of the, auxochromes and the consequent increased resonance. A good example of the value of the theory is given by the triphenylmethane dyes, which may be regarded as derivatives of fuchsonimine (XI). This



compound is colourless, while its hydrochloride (XII) is orange red and dyes tanned cotton. If now, a second amino group is introduced into one of the vacant para positions, resonance between forms XIII and XIV occurs and we have the dyestuff *Doebner's Violet*.



Other examples will be found in the text.

In conclusion it may be noted that the theory of resonance is still in process of development and that time must elapse before its scope and limitations are properly understood.

10. Optical Behaviour

A. MOLECULAR REFRACTION

The molecular refraction of a substance is the product of the specific refraction into the molecular weight :

(where n =index of refraction, M =molecular weight, d =density).

¹ C. R. Bury, *J.A.C.S.*, 1935, 57, 2115; Schwarzenbach, *Helv. Chim. Acta*, 1937, ² 490, 498, 627.

In general it is an additive property, the molecular refraction of a compound being equal to the sum of the atomic refractions of the elements contained in it.

The following table gives the atomic refractions of some of the elements, in the one column as referred to sodium light, and in the other to the red hydrogen line :—

Element.	Sodium Light.	Red hydrogen Line.	
C	2.500	2.365	Carbon in a single bond.
H	1.051	1.103	
O'	1.525	1.506	
O"	2.211	2.328	Hydroxylic oxygen.
O<	1.643	1.655	O in the carbonyl group.
Cl	5.998	6.014	O in simple ethers.
Br	8.927	8.863	
I	14.120	13.808	
=	1.707	1.836	Double bond between two carbon atoms.
≡	...	2.220	Triple carbon linking.

The atomic refraction of nitrogen varies considerably according to the compound in which it occurs. The extreme values are 2.446 and 4.363 for sodium light, and 2.311 and 4.105 for the red hydrogen line.

From the above data it is possible to calculate the molecular refraction of a series of compounds by summation of the atomic refractions, and for the most part the values so obtained are in good agreement with those determined by experiment.

As may be seen from the table, the atomic refraction of polyvalent elements, such as carbon or oxygen, varies with the state of combination, and from the experimentally determined molecular refraction it is therefore possible to draw conclusions as to the constitution of a compound. Valuable work in this sphere has been carried out by Brühl and Auwers who have shown that molecular refraction and dispersion are partly additive and partly structural in character.

According to Brühl the molecular refraction also affords a means of distinguishing between the keto and enol forms of tautomeric compounds, since the double bond of the enol form betrays itself in the characteristic value of the ethylene bond.

B. OPTICAL ROTATION ¹

The theoretical treatment of optical activity has already been given in connection with stereoisomerism, see p. 26 *et seq.*

Specific Rotation.—An exact quantitative expression of the degree of activity of a fluid or dissolved compound was made possible by the introduction of the term *specific rotation* $[\alpha]$.

The value of the specific rotation is given by an expression such as

$$[\alpha]_{\lambda}^t = \frac{\alpha \times 100}{l \times c} \quad \text{or} \quad \frac{\alpha \times 100}{l \times d \times p}$$

¹ T. M. Lowry, *Optical Rotatory Power* (Longmans, 1935).

in which λ represents the wavelength of light employed, α = angle of rotation observed, t = temperature, l = length in decimetres of liquid traversed, c = number of grams of substance contained in 100 c.c. of the solution, d = density of solution, and p = number of grams substance in 100 grams of solution. A clockwise or dextro rotation as seen by an observer using the polarimeter is written as +, and a counter-clockwise or laevo rotation as -.

The product of the specific rotation and the molecular weight M is known as the *molecular rotation*, and is represented as follows :

$$[M] = \frac{[\alpha]M}{100}$$

In this case the hundredth part of the product is taken, in order to avoid unwieldy numbers.

Variation in the Rotation with Experimental Conditions.—Owing to the great interest aroused in stereochemical problems a considerable amount of experimental data dealing with optical rotation has gradually been accumulated. In most cases (with the exception of aqueous solutions of certain sugars) the specific rotation varies with the concentration of the solution, and frequently also with the nature of the solvent employed. Thus, for example, L-tartaric acid is dextrorotatory in aqueous solution but laevorotatory when dissolved in a mixture of ether and acetone.

In some instances the rotation of a freshly prepared solution of an active substance is found to change progressively with time, until equilibrium is finally attained. This is known as *mutarotation* and is well illustrated in the case of glucose (see glucose, p. 312). The alteration in activity goes hand in hand with an intramolecular change.

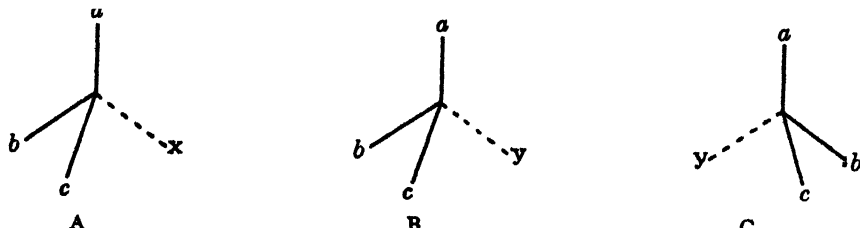
Every chemical action undergone by an active compound produces a visible change in the rotation, the magnitude and direction of which is dependent on the constitution of the active molecule, as well as on the chemical character of the reagent employed.

The greatest alterations in specific rotation which have so far been effected by chemical action on a given asymmetric carbon atom occur when certain active hydroxy compounds are treated with inorganic substances to form complexes and cyclic derivatives. In these cases the degree of asymmetry, and therewith the optical properties, are often fundamentally modified.

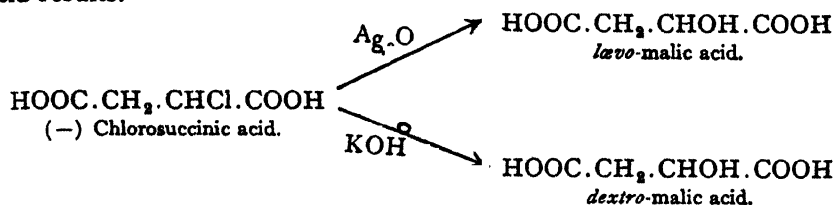
Walden Inversion.—When a group in an organic compound is replaced by a second group it is generally assumed that, unless there is evidence of isomeric change, etc., the substituent occupies the same position in the molecule as the replaced group. For example, an optically active compound (A) in the simplest case will give compound (B). This indeed, frequently happens, but often substitution is accompanied by configurational changes. A, for example, may give C and not B.

This configurational change is known as an *optical inversion* or the *Walden Inversion*, after its discoverer, Paul Walden. A simple example

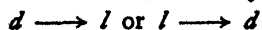
is afforded by the replacement of the chlorine atom in *l*-chlorosuccinic acid by the hydroxyl group to give malic acid.¹ If silver oxide is used



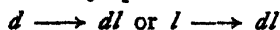
l-malic acid is obtained, while with potassium hydroxide the *dextro*-acid results.



In one case a simple replacement of chlorine by hydroxyl occurs; in the other a replacement accompanied by molecular rearrangement resulting in the production of the mirror-image of the expected structure. Which reaction is "normal" and which "abnormal" cannot be determined without further data. There is evidence to show that in the above example the configurational change occurs when potassium hydroxide is used, and this is indicated by the sign \longrightarrow . If the *l*-malic acid is treated with phosphorus pentachloride *dextro*-chlorosuccinic acid is obtained. In other words, by a two-stage process an optically active compound has been converted into its antipode. The yield and purity of the product are good. The method is therefore quite different from that of racemisation in which an optically active compound is converted into its optical isomer, but only to the extent of 50 per cent.

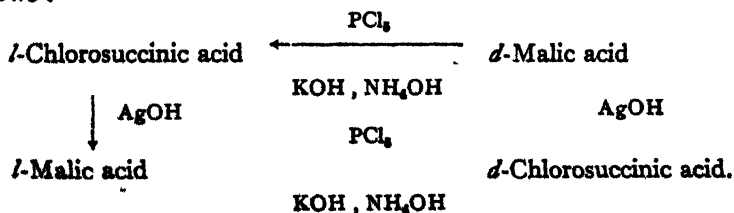


Walden Inversion



Racemisation

The process may be continued and a complete optical cycle obtained as follows :—

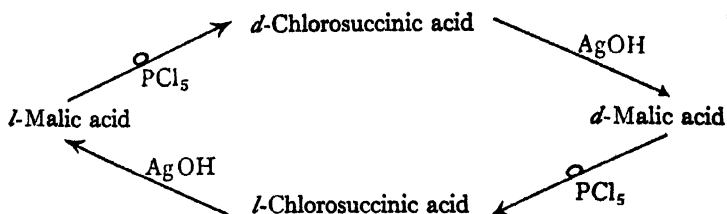


Many other similar cycles have been studied.

¹ See Walden, *Optische Umkehrerscheinungen* (Vieweg and Son, Brunswick, 1920); H. B. Watson, *Theories of Organic Chemistry* (Oxford University Press, 1941), p. 235; T. Wagner-Jauregg, in Freudenberg's *Stereochemistry*, p. 883.

It must be noted that change of sign is no indication that inversion has occurred, for compounds of similar configuration do not necessarily have the same sign of rotation; the mere fact that *levo*-chlorosuccinic acid gives *dextro*-malic acid is no indication of inversion. It follows that two reactions are always necessary to establish the occurrence of a Walden inversion.

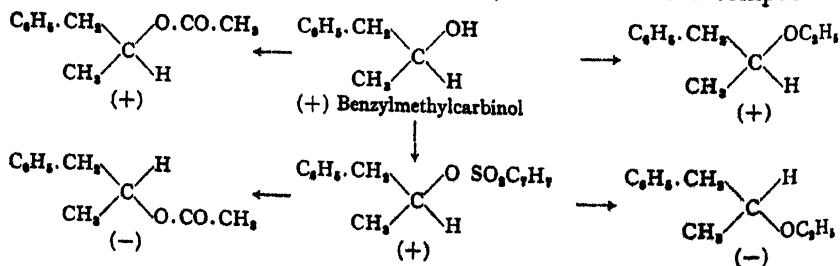
According to R. Kuhn and T. Wagner-Jauregg¹ the classical chlorosuccinic acid-malic acid cycle proceeds as in the following scheme:—



A more rigid proof of the above conclusions is still required.

It has been shown in most cases that the Walden inversion involves substitution on the asymmetric carbon atom. It is of the greatest importance, therefore, in configurational determinations by means of optical rotation measurements that the chemical changes involved should be brought about without disruption of the bonds at the asymmetric centre. Instances of this are found in configurational determinations in the sugar and amino-acid series (pp. 238, 302).

Mechanism of the Walden Inversion.²—Many investigations have been carried out to throw light on the nature of the Walden inversion. Among the chemical researches may be mentioned those of Phillips and Kenyon.³ The work of these authors established in many cases the actual steps in a series of reactions at which inversion occurs. (+)-Benzylmethylcarbinol gives acetyl and ethyl derivatives with the same sign of rotation. It follows, since no valence bond of the asymmetric carbon has been disturbed, that these three compounds



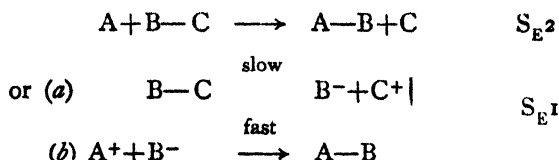
possess the same configuration as well as the same sign of rotation. The carbinol, however, may be converted into the *p*-toluenesulphonyl ester, which may be made to give *levo*-rotating acetyl and ethyl

¹ Ber., 1928, 51, 504. ² H. B. Watson, Ann. Reports, 1938, 35, 218. ³ Phillips, J., 1923, 123, 44; Kenyon, Phillips, and Turley, J., 1925, 127, 399.

derivatives. It is therefore established with a fair amount of certainty that inversion occurs when the toluenesulphonyl group is replaced by acetyl or ethyl radicals.

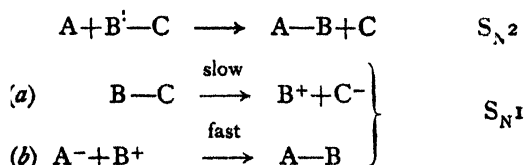
A fuller understanding of the mechanism of the Walden Inversion has resulted from the combination of kinetic and polarimetric measurements by Ingold, Hughes, and others. The Walden Inversion involves the replacement of one atom or group in a molecule by another atom or group. Reactions of this type may be either monomolecular or bimolecular and may be brought about either by electrophilic or nucleophilic attack. Suppose we consider the reaction $A+B-C \rightarrow A-B+C$. If A is an electrophilic reagent the course of the reaction may be represented either by S_E2 or S_E1 .

Electrophilic Substitution



If A is nucleophilic similar alternatives are available.

Nucleophilic Substitution

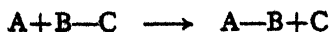


The first reaction in each of the above substitutions is obviously bimolecular, while in the second the reaction is monomolecular, the rate of the reaction being the rate of ionisation of the compound BC.

Ingold, Hughes *et al.*¹ come to the following important conclusions.

- (1) *Bimolecular substitutions (S_E2 and S_N2) are invariably accompanied by optical inversion.*
- (2) *Monomolecular substitutions (S_E1 and S_N1) may lead to inversion, retention of configuration, or racemisation depending on a number of factors.*

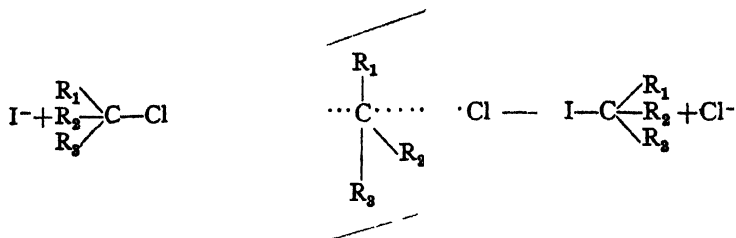
The occurrence of optical inversion as the result of bimolecular substitution is readily understood in terms of modern theory. In the reaction



the most favourable attack by A is along the linkage axis keeping as far

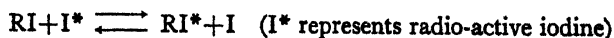
¹ A. W. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J.*, 1937 1252.

from C as possible. There is no sudden breaking of the B—C bond, but a gradual loosening as the A—B bond forms. Finally A is completely bound to B and C is completely separated. For example, in the replacement of chlorine in an alkyl chloride by iodine, an intermediate complex is formed in which chloride and iodide ions are loosely bound to the carbon, while the three alkyl groups are pulled into a plane which contains in addition the carbon atom. At the end of the process the chloride ion splits off and the alkyl groups move to their final positions.

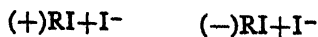


The net result is that the molecule has been turned inside out "like an umbrella in a strong wind." If the initial compound is optically active the inversion of configuration is shown by change of sign of the optical rotatory power. The inversion of (+)-benzylmethylcarbinol *p*-toluene sulphonate by acetate or ethylate ion cited above is a concrete example of inversion by nucleophilic attack.

Elegant experimental confirmation of the correctness of the theory comes from the application of radio-active indicators,¹ and is best explained by an example. *sec*-*n*-Octyl iodide when dissolved in acetone reacts with radio-active iodide ion.



The rate of the reaction can be followed by measuring the radio-activity of the octyl iodide at given intervals. The octyl iodide also undergoes racemisation under the influence of iodide ions according to the equation



If displacement is invariably accompanied by inversion, the rates of iodine exchange and of racemisation should be identical. This was found to be so.

The consequences of monomolecular reactions are, as already stated, more complicated but are frequently understandable. For instance, in nucleophilic substitution by the monomolecular mechanism the first stage is the formation of a carbonium ion (positive ion) which is flat and thus symmetrical. Substitution can in consequence occur at either side giving a racemic mixture.

¹ E. D. Hughes, F. Juliusberger, S. Masterman, B. Topley and J. Weiss, *J.*, 1935, 15

Ultra-violet and Infra-red Absorption Spectra¹

The absorption of light has been intensively studied not only in the visible region (wave-length = 4000-8000 Å), but also in the ultra-violet (10-4000 Å) and the infra-red (above 8000 Å). Modern instruments enable us to measure quantitatively these absorptions: that is, we can measure accurately both the wave-length at which absorption occurs and the absorption intensity. This has led to the general use of spectrometers in many fields of organic research.

Ultra-violet Absorption

The absorption of light by a molecule in the visible or ultra-violet region is due to transfer of energy from the light to the electrons of the molecule. Ultra-violet absorption spectra are in consequence often termed *electronic spectra*. Most of the results recorded at the present day are in the *near ultra-violet* (2000-4000 Å), since measurements at a smaller wave-length demand special technique and apparatus. This is understandable when it is realised that nearly all substances including quartz and air are opaque to radiation with wave-length below 2000 Å.

Most measurements are made in dilute solutions of saturated hydrocarbons such as hexane, heptane, or cyclohexane which are transparent to ultra-violet light. The wave-length is given by a scale on the recording plate and the absorption intensity at any given wave-length is obtained from the following equation.

$$\log \frac{I_0}{I} = \epsilon cd$$

I_0 : intensity of incident light

I = intensity of light after absorption

ϵ = molecular extinction coefficient

c = concentration in g. moles/litre

d = length of absorbing layer in cm.

In many instruments the ratio $\log \frac{I_0}{I}$ (known as the *density*) is directly recorded, and the molecular extinction coefficient which is a measure of the absorption intensity, is then easily calculated. It may have values between 1 and 50,000 or 60,000, and to avoid the use of such large figures the absorption intensity is often measured by $\log \epsilon$.

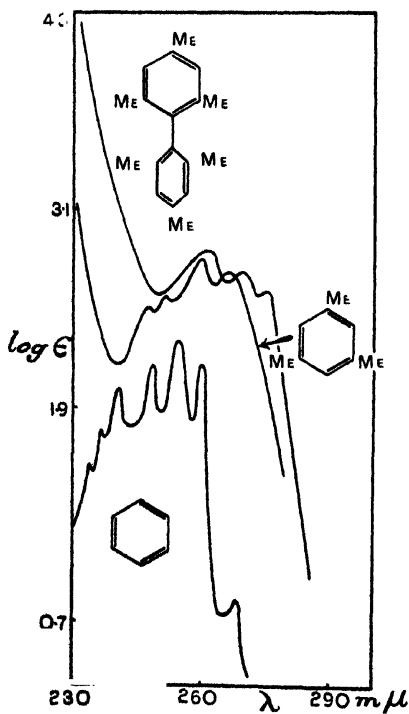
The absorption of a substance is most conveniently characterised by plotting the intensity of absorption (ϵ or $\log \epsilon$) against the wave-length expressed in Å (10^{-8} cm.) or $m\mu$ (10^{-7} cm.) or the reciprocal wave-length known as the *wave-number*. In this way absorption curves such as those shown in the figure below are obtained. Frequently the absorption is described by giving the wave-lengths and extinction coefficients at which maximum absorption occurs (λ_{\max} , ϵ_{\max}).

¹ For general surveys see "Ultra-violet Light Absorption," E. A. Braude, *Ann. Reports*, 1945, 42, 106. *Ultra-violet Spectra of Aromatic Compounds* by R. A. Friedel and M. Orchin (Chapman and Hall, London, 1951). *An Introduction to Electronic Absorption* by A. E. Hillam and E. S. Stern.

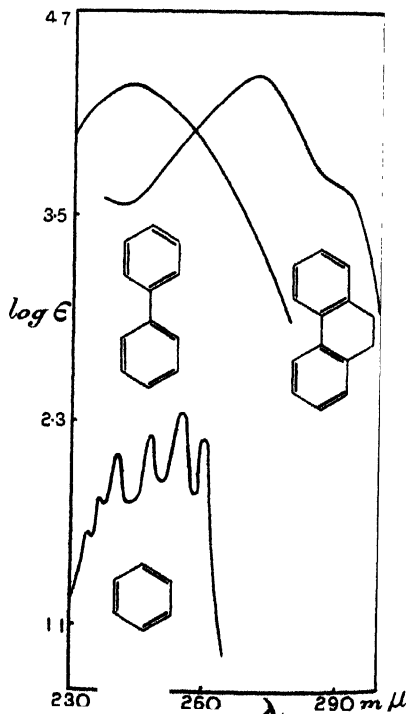
It must be stressed that our knowledge of the relationship between absorption and chemical constitution is largely empirical and satisfactory interpretation of the absorption curves is frequently difficult. Nevertheless, absorption studies have proved extremely valuable in problems of constitution and identification. Some examples will be found below and in later chapters.

Ultra-violet Absorption and Molecular Constitution.—Certain groups or chromophores in a molecule confer absorption in particular regions of the spectrum. Among what we may term the *ultra-violet chromophores* are the following :—

$>C=C<$	λ max.
$>C=O$	180 $m\mu$
$-N=N-$	280
$-NO_2$	345
	370



Ultra-violet absorption spectra of benzene, mesitylene, and dimesitylene.



Ultra-violet absorption spectra of diphenyl, 9:10-dihydrophenanthrene, and benzene.

These chromophores or functional groups may thus be easily detected by the spectrometer. Even more valuable information is derived from the study of compounds with two or more chromophores. Such groups if separated by one or more saturated groups (CH_2 , etc.) absorb indepen-

dently and characteristically. Otherwise group interaction occurs giving rise to modified spectra. For example, oct-3-ene shows the expected absorption and intensity of an olefinic derivative, and the double bonds in diallyl absorb at the same wave-length, but with more than twice the intensity. On the other hand, in butadiene a displacement of the absorption maximum of about $40\text{ m}\mu$ shows decisively the conjugation effect.

		λ max.	ϵ max.
Oct-3-ene	$\text{CH}_3(\text{CH}_2)_3\text{CH}:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_3$	$185\text{ m}\mu$	8,000
Diallyl	$\text{CH}_2:\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}:\text{CH}_2$	175	20,000
Butadiene	$\text{CH}_2:\text{CH}\cdot\text{CH}:\text{CH}_2$	217	20,900

Generalising, it can be stated that *increasing conjugation results in increase of the wave-length of maximum absorption and increase of the intensity.*

Use is frequently made of the fact that compounds related in structure exhibit similar absorption. For example, diphenyl and 9 : 10-dihydrophenanthrene have very similar absorption curves (see p. 88). The two compounds differ in structure only by the bridge of two methylene groups and these saturated groups have no chromophoric properties.

Fine Structure.—Ultra-violet absorption sometimes gives us insight into the fine structure of organic compounds. This is well illustrated by the diphenyl molecule. The interaction between the two nuclei is clearly shown by the difference of the absorption curve from that of benzene. It is probable that such interaction is possible only when both rings are co-planar and this conjecture is supported by the similarity already noted between the absorption of diphenyl and 9 : 10-dihydrophenanthrene. In the latter compound the benzene nuclei are forced into one plane by the methylene bridge. Further evidence is supplied by the striking similarity of the absorption curves of mesitylene and dimesitylene. In the second compound the blocking "ortho" groups prevent planarity of the molecule and in consequence interaction between the nuclei does not take place.

Infra-red Absorption¹

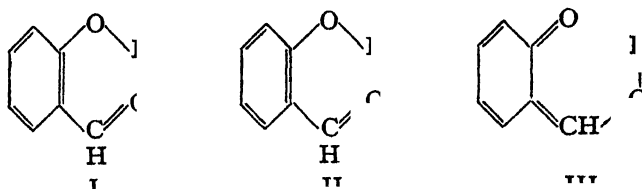
Absorption in the infra-red region is due to molecular vibration and rotation. Whilst it is true that the spectra are characteristic of the molecule as a whole, certain absorptions are associated with groups such as the hydroxyl and amino. Hence infra-red absorption spectra are frequently measured to show the presence or absence of these groups (see below), or to distinguish between closely related radicals. An example is given on p. 482 of the differentiation between the cyano ($\text{R}\cdot\text{C}:\text{N}$) and the isocyano ($\text{R}\cdot\text{N}:\text{C}$) groups by this method.

The infra-red region covers a wide range of the electro-magnetic spectrum. The region most commonly considered lies between 2 and

¹ "The Scope and Limitations of Infra-Red Measurements in Chemistry," H. W. Thomson, *J.*, 1944, 183.

25 μ . The absorption bands are given either in terms of *wave-length* (μ units) or of *wave numbers*, which are the reciprocals of the wave lengths in cm. Absorption is depicted by curves similar to those described for ultra-violet absorption.

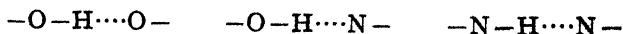
Infra-red absorption has provided experimental evidence for the fine-structure of many substances. This is well illustrated by the *ortho* substituted phenols. Sidgwick and Callow pointed out that the properties of many of these differed radically from those of the corresponding *meta* and *para* isomers. This occurs only when the substituent contains an electron-donating atom such as oxygen. Salicylaldehyde, for instance, is regarded as having formula I, and this is simply another way of saying it is a resonance hybrid derived from the contributing structures II and



III. The formation of this *intramolecular hydrogen bond* to give a *chelate ring* clearly modifies the properties of the hydroxyl group, dependent as they are on a "free" hydrogen atom. As a result the compound will be less soluble in polar solvents such as water and more soluble in non-polar solvents such as benzene, etc.

The presence of these *hydrogen bonds* is confirmed by infra-red absorption measurements.¹ The OH group has an absorption band in the region of 7000 cm^{-1} and this band appears only in those compounds such as phenol incapable of forming hydrogen bonds, but is completely absent in salicylaldehyde, etc., where hydrogen bonds are to be anticipated.

In hydrogen bonding the hydrogen atom acts as a link between two electro-negative elements such as oxygen or nitrogen.



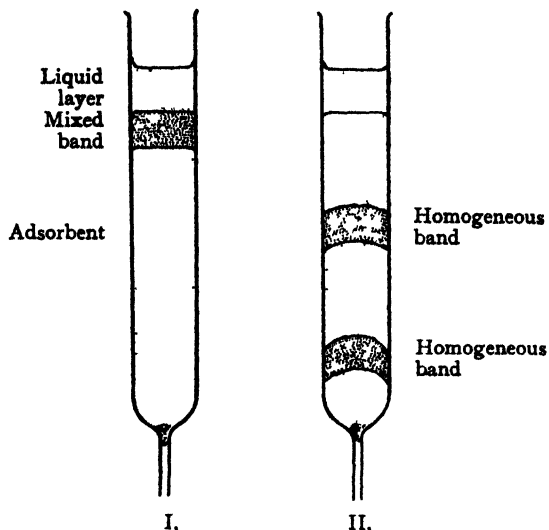
For hydrogen bonding to occur the two atoms must not be separated by more than 3.4 Å.

11. Chromatography

A process of the greatest value to the organic chemist for the separation of mixtures, especially of complex coloured substances, has been developed in chromatography or chromatographic analysis.² In this

¹ Hilbert, Wulf, Hendricks and Liddel, *J.A.C.S.*, 1935, 57, 1464; *J.A.C.S.*, 1936, 58, 548.
² *Principles and Practice of Chromatography*, by Zechmeister and Chohnoky, translated by A. L. Bacharach and F. A. Robinson (Chapman and Hall, 1941); *Chromatographic Analysis*, A. H. Cook (Institute of Chemistry, 1941).

method, which originated in the work of the Russian botanist Tswett in 1906, the mixture is dissolved in a selected solvent (*e.g.* petroleum or benzene) and the solution is allowed to flow down a vertical tube which has been firmly packed with a suitable adsorbent (*e.g.* powdered calcium



carbonate or alumina) covered with the same solvent. Frequently the flow of liquid is assisted by use of gentle suction. In this way the more strongly adsorbed components of the mixture are removed from the solution to form a coloured band at the top of the tube (I).

The column containing the adsorbed material, which is known as the **chromatogram**, is next *developed* by washing continuously with a solvent, not necessarily the same as that used for making up the solution, when several changes normally occur. The coloured band moves slowly down the tube, spreads out and finally divides into a number of coloured bands separated by zones of white adsorbent (II). This development is due to the fact that for each component in the mixture a definite equilibrium exists between the compound in the adsorbed and dissolved states, dependent on its coefficient of adsorption. Since there is a constant flow of liquid down the tube, the adsorbed particles on passing into solution are carried a short distance downwards before being redeposited on a fresh surface of the adsorbing material. Strongly adsorbed compounds are only slowly brought into solution by the solvent, and are then rapidly deposited again. The adsorbed layer of such a compound thus travels slowly. Weakly adsorbed compounds on the other hand move rapidly. Each adsorbed compound therefore moves down the tube with a speed which is inversely related to its coefficient of adsorption, and for this reason the original mixed band eventually separates into a number of individual bands, each of which in general constitutes a chemically pure component having its own characteristic colour.

Complete separation and recovery of the components may be effected in one of two ways. The solvent may be drained off from the **developed chromatogram** and the still moist column of adsorbent extruded from the tube; individual coloured bands can then be cut out with a spatula and the adsorbed material *eluted* by means of a suitable solvent (*e.g.* alcohol or chloroform). Or the flow of pure solvent may be continued until bands are washed out one by one from the lower end of the tube, the various fractions are then collected separately and the solids recovered by evaporation. This second method requires a much longer time and with sensitive compounds may result in loss owing to interaction between the adsorbed material and the adsorbent.

Chromatographic analysis thus involves the following series of operations. (1) Adsorption on a selected adsorbent. (2) Development by washing. (3) Separation of the individual bands. (4) Elution of each component and recovery by evaporation. (5) In difficult cases where the bands do not separate completely the eluted products may be submitted to a second treatment.

In his original work Tswett only used exceedingly small quantities. His conclusions were drawn from the appearance of the developed chromatogram and no attempt was made to isolate or analyse the individual components. Nevertheless he was the first to show that two different chlorophylls and two different phaeophytins existed, and to suggest that leaf carotene was a mixture which might eventually be separated by the chromatographic method. Unfortunately, the principles of chromatography as published by Tswett in 1910 were written in the Russian language and for this reason did not become generally known to chemists until 1931 onwards, in which year Kuhn, Winterstein and Lederer applied them on a preparative scale to the chemistry of the polyene pigments (see carotene).

By special devices the process has been extended to the **separation of colourless solids and liquids**. In 1934 Winterstein and Karrer independently showed that in ultraviolet light many compounds exhibit a characteristic fluorescence on the chromatogram, by means of which they may be developed and separated. Certain other colourless compounds can be converted into coloured derivatives before adsorption. Ketones, for example, yield coloured dinitrophenyl-hydrazones, which may be separated chromatographically and the hydrazone groups subsequently removed by hydrolysis. A colourless chromatogram may sometimes be rendered visible by means of a colour reaction, *e.g.* by extruding the developed column and testing with a selected indicator. Thus mixtures of amines separated in this way are examined by lightly brushing the column of adsorbent with an aqueous solution of sulphanilic acid and sodium nitrite, when coloured streaks of bright azo-dyes indicate the positions of the individual bands. After cutting up the column, the narrow surface layer of dyestuff is scraped off each section before recovering the bulk of the adsorbed amine.

Preliminary experiments are required in order to determine the best conditions for any mixture. The adsorption coefficient depends on a number of factors, including the temperature, the chemical nature and physical state of the adsorbent and the nature of the solvent, and it is necessary that these are so adjusted that the adsorbed material is held firmly, although not so strongly as to prevent full development on washing. Among the more commonly used adsorbents are *alumina*, *fuller's earth*, *talc*, *gypsum*, *calcium carbonate*, *magnesia*, *lime* and *sugar*. Alumina adsorbs strongly and has been employed for a large number of separations; sugar is a relatively weak agent. As solvents, *petroleum* (b.p. 60-80°) and *benzene* are most frequently used or a suitable mixture of the two. In general, organic compounds are most readily adsorbed from non-polar or very weakly polar solvents; the final elution, on the other hand, is best effected with polar liquids.

Development by washing can often be achieved by use of the same solvent, if necessary with the addition of a small amount (1-2 per cent.) of alcohol. Benzene commonly leads to a more rapid development than petroleum, and adjustment can often be made by using mixtures of these solvents. After cutting out the individual bands, the final elution is effected by means of alcohol, chloroform or pyridine.

Chromatography has proved of the utmost value in biochemical research, for example in the separation of colouring matters of plants, of vitamins and of hormones. Many references to its use will be found throughout the course of this book. The highly selective nature of the process is illustrated by the *partial resolution of racemic p-phenylene-bisimino-camphor* which was carried out by Rule and Henderson¹ using a tube filled with the optically active adsorbent, D-lactose, and by the selective adsorption of the diastereoisomerides (—)-menthyl (+)-mandelate and (—)-menthyl (—)-mandelate on alumina.² The complete resolution of Tröger's Base has been effected successfully by the chromatographic method.

In addition to its use for the *separation of complex mixtures*, chromatography is employed in the following ways. (1) As a *test of homogeneity*: a pure compound gives a single adsorption band, which does not break up into two or more bands on washing, even when the adsorbent and solvent are changed. (2) As a sensitive *test for the identity or non-identity of two substances*: the mixed compounds if identical yield a single band. This method is particularly valuable in cases where the compounds have no characteristic melting-points. (3) For the *concentration of products* occurring at great dilution in a natural source. Koschura isolated the colouring matter uropterin from urine, in which the concentration is only 1 part in a million, by adsorption followed by elution and subsequent purification by the chromatographic method.

A development similar in technique but different in principle is that

¹ H. G. Rule and G. M. Henderson, *J.*, 1939, 1568.
² *J.*, 1942, 611

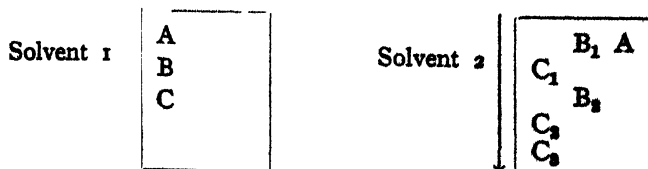
² M. M. Jamieson and E. E. Turner,

of **partition chromatography** introduced by Martin and Synge. It is based on the differences of partition coefficients of substances between immiscible liquids such as water and chloroform. Organic chemists have long used such differences to separate mixtures, but the new method affords such an increase in efficiency that it may be applied to the separation of very small quantities of material.

Silica-gel can adsorb some 50 per cent. of water without becoming "wet." A column of this hydrated silica-gel is prepared in the usual manner and a solution in chloroform (or other solvent insoluble in water) of the mixture to be separated is dropped through it. The column is developed by more solvent. As a result of the partitioning between the "held" water column and the "flowing" solvent, those components of the mixture which are more soluble in water remain at the top of the column, while those more soluble in the solvent collect at the foot. Manipulation is frequently assisted by the use of indicators. For instance, in the very successful separation of acetylated amino-acids, methyl orange is added. Most of the column is coloured faintly yellow, but the acetyl amino-acid zones are pink.

If the column has been properly prepared no adsorption occurs on the silica-gel. The separations are based on solubility not on adsorption differences.

A most ingenious development of partition chromatography is that of Martin, who applied it to the separation of amino-acids. Instead of silica-gel it is possible to use a strip of filter paper to support the aqueous phase. To prevent evaporation this is maintained in an atmosphere of the vapours of water and solvent. A drop of the solution to be analysed is applied at the top of the strip and developed by a suitable solvent. The paper is dried and sprayed with ninhydrin solution and the position of each amino-acid is then revealed by a blue spot. Separation, however, is not always complete, and Martin overcame this difficulty by using a "two-dimensional" chromatogram consisting of a sheet of filter paper. The solution of amino-acids is applied at one corner and developed in one direction. The paper is then dried, turned through 90° , and developed with a second solvent. Amino-acids not separated by the first solvent are separated by the second. As a result each amino-acid occupies a separate, characteristic position on the paper. In the diagrams, development with the solvent 1 gives a separation into three "zones" A, B, and C. By turning the paper at right angles and developing with a second solvent, A is shown to be homogeneous, but B and C mixtures of B_1 and B_2 and C_1 , C_2 , C_3 respectively.



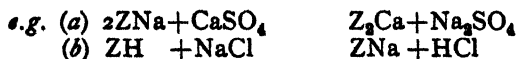
Some idea of the efficiency of the method may be obtained from the separation and identification of 22 amino-acids from only 400 μ g. of hydrolysed wool protein.

12. Ion Exchange Resins

A principle which for decades has been used in the softening of water has recently been applied in other fields and promises to furnish an important method for the separation and purification of organic compounds. This is due to the discovery of ion exchange resins¹ at the Chemical Research Laboratory, Teddington, in 1935. Adams and Holmes showed that when a formaldehyde-polyhydric phenolic resin is placed in a solution of a salt some of its ionisable hydrogen atoms are replaced by metallic ions. This hydrogen-metal exchange opens up great possibilities since these resins (unlike the zeolites) are stable in acid solution. Adams and Holmes also found that a basic resin, made by using amines instead of phenols in the resin formation, removed acids from solution. Subsequent development has led to the preparation of resins with stronger basic or acidic properties, and which at the same time effect quick exchange, are chemically stable, and possess sufficient mechanical strength. By ion exchange, as these examples show, we mean the reversible interchange of ions between a liquid and a solid, involving no appreciable structural change of the solid.

There are two types of exchangers.

1. **Cation Exchangers.**—These are usually sulphonated phenol-formaldehyde resins, the positive ions of which are exchanged for positive ions in the solution :—



The "used" exchanger can be regenerated by washing with sulphuric acid.

2. **Anion Exchangers** are often polyamine-formaldehyde resins which are used for removal of acids from solution. This process is not fully understood, but is probably adsorption of the acid on the resin rather than exchange of negative ions



The resin can be reactivated and the acid removed by washing with alkali.

Recent work confirms the hypothesis that these synthetic resins behave as completely porous gels in which all the active groups can function.

A simple example of the application of ion exchange is the removal of formic acid from formaldehyde by an acid adsorbing resin. This is

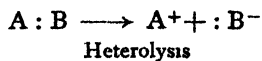
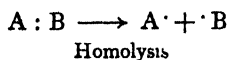
¹ B. C. Adams and G. L. Holmes, *J.S.C.I.*, 1935, 54, 1; J. F. Duncan and B. A. J. Lester, *Quarterly Reviews*, 1948, 2, 307.

of considerable value in the synthetic plastic industry where acid-free formaldehyde is required. Other applications of the method are given in the text.

In recent years physical methods have supplemented those of the organic chemist, and it is difficult to over-estimate the importance of the results obtained by X-ray analysis, absorption spectra measurements, sedimentation rates with the ultra-centrifuge, etc. Reference to such methods will be found in other parts of the book.

MOLECULES, IONS, AND FREE RADICALS IN ORGANIC REACTIONS¹

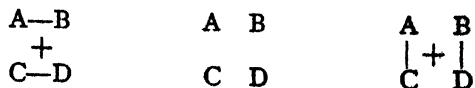
Most organic reactions are either reactions between molecules or between molecules and ions, but it is now recognised that many occur between molecules and *free radicals* (see below). Whether ions or free radicals occur depends on the nature of the bond fission of the molecules taking part. A covalent bond may undergo *homolysis* or *heterolysis* (Ingold) according to whether the cleavage is symmetrical or unsymmetrical.



In homolytic fission one electron (represented by a dot) accompanies each of the fission products and neutral free radicals result. In heterolytic fission, on the other hand, both electrons attach themselves to one of the products and ions result. It is of the utmost importance that the part played by molecules, ions, or free radicals be determined for any given reaction: then and only then can the true course of the reaction be understood.

Molecular Reactions

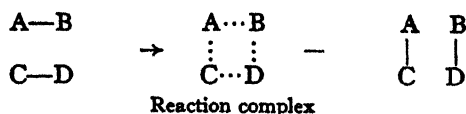
A great many reactions occur, so far as we know, between molecules. The essential feature of this was formerly pictured to be a sudden breaking of old linkages followed by formation of new linkages. For example, in the reaction :—



the bonds of AB and CD are disrupted and the dissociated fragments then combine to form AC and BD. It is now certain that this sudden dissociation of bonds does not occur and that instead there is a gradual transition, the loosening of the bonds of the reactants being proportional

¹ "Homolytic Reactions," D. H. Hey, *Ann. Reports*, 1944, 42, 181. "Free Radicals," D. H. Hey, *Ann. Reports*, 1940, 37, 250. D. H. Hey and W. A. Waters, *Chem. Reviews*, 1937, 21, 169.

to the formation of new bonds in the products. Another way of expressing this is to say that the reaction proceeds via a *Reaction Complex* or *Activated Complex* in which the bonds are scarcely localised.



The energy required for a reaction of this type is much less than that required for one involving complete dissociation of the reactant molecules. It must be noted that the reaction complex has only a transient existence and cannot be isolated.

Ionic Reactions

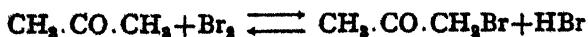
The ionic reactions of inorganic chemistry are characterised by their great speed, many of them being instantaneous or at least too fast for measurement. Organic reactions generally occur with measurable velocity and were therefore assumed to belong to the molecular category. Modern research and particularly the fact that many reactions occur only in the presence of acidic or basic catalysts has provided strong evidence that many of the well-known organic reactions are ionic. This has led to a satisfactory explanation of puzzling reaction velocity results and has provided a picture of the important part played by the catalyst.

Before proceeding further it is essential to recall the modern definition of acids and bases (p. 67), according to which *an acid is a substance capable of yielding a hydrogen ion or proton, and a base one capable of accepting a proton.*

The modern definition greatly extends the list of acids and more particularly of bases and is clearly independent of the presence or absence of electric charge.

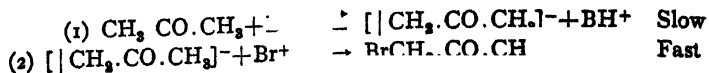
Acids.	Bases.
HCl	Cl ⁻
NH ₄ ⁺	NH ₃
CH ₃ COOH	CH ₃ COO ⁻
H ₃ O ⁺	H ₂ O
HSO ₄ ⁻	SO ₄ ²⁻

This picture of acidic and basic function has proved very fruitful in the study of the mechanism of organic reactions, and as an illustration the pioneer work of Lapworth on the bromination of acetone will be considered. This reaction, represented by the following equation



has two notable features. According to the law of mass action the rate of this reaction should be proportional to the concentrations of the acetone and bromine. Lapworth found, however, that the rate is proportional

to the concentration of the acetone but is independent of the concentration of the bromine. Secondly, the speed of the reaction is proportional to the concentration of added acids or bases. These facts are adequately explained by a two-stage reaction, as shown by the following equations for the base-catalysed bromination of acetone (B stands for the base).



The first reaction occurs with measurable speed since the reaction is between a base and a very weak acid (acetone), but the second reaction takes place instantaneously. The overall rate of the reaction is therefore that of the formation of the intermediate anion, and this is termed the *rate-determining step*. In consequence, the rate of the reaction is proportional to the concentration of the acetone and base and is independent of that of the bromine.

This mechanism of the reaction has the advantage not only of explaining the reaction kinetics, but also of defining the function of the catalyst. The modern definition of bases explains why the reaction is catalysed by the acetate ion, etc. Similar mechanisms have been advanced for other reactions of this type, particularly those taking place in water or other ionising solvent and which are catalysed by ions (acids or bases).

Homolytic Reactions

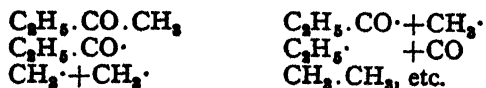
As already pointed out there is a second way in which a covalent bond may be broken, giving rise not to ions but to free radicals. These *organic or free radicals* are conveniently defined by Wieland in the following terms: *Free radicals are complexes of abnormal valency, which possess additive properties, but do not carry an electric charge and are not free ions*.

The idea of radicals is not new and was introduced by Lavoisier as long ago as 1785, and many organic chemists, Gay-Lussac, Bunsen, Frankland, etc., believing the isolation of such radicals to be possible, attempted their preparation. Although obtaining many results of importance they did not succeed in their immediate task, and towards the end of the nineteenth century considerable scepticism existed as to the possibility of isolating free radicals. Doubt was finally dispelled in 1900 when Moses Gomberg of the University of Michigan announced the discovery of the triphenylmethyl radical, $\text{Ph}_3\text{C}\cdot$, and thereby opened up a rich field for theory and experiment.

In addition to trivalent carbon radicals, divalent and quadravalent nitrogen, univalent oxygen, and univalent sulphur radicals are also known.

Gaseous reactions are mostly homolytic. Norrish, for example, concluded that the photodecomposition of ketones into carbon monoxide and hydrocarbons proceeds via free radicals. Thus methyl ethyl ketone on irradiation with light of wave-length 2900 Å breaks down into the methyl and propionyl radicals, the latter yielding the ethyl radical and

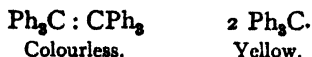
carbon monoxide. The radicals then combine to give a mixture of ethane, propane, and butane.



It is only recently, however, that D. H. Hey, W. A. Waters, etc., have shown that many reactions *in solution* are due primarily to homolytic fission with the production of free radicals (see, for example, pp. 446, 483).

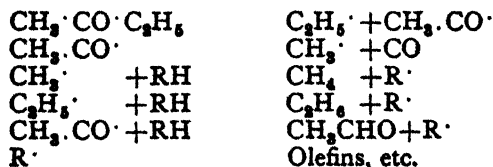
The existence of free radicals is generally recognised not by their isolation but by their properties, some of which are given below.

(1) Formation of free radicals is sometimes accompanied by *colour* formation, a result not unexpected in a change from a saturated molecule to a highly unsaturated radical. The colourless hexaphenylethane, for example, yields the yellow triphenylmethyl radical.



(2) As would be anticipated from their unsaturated character, free radicals are chemically *extremely reactive*, so much so that many have an exceedingly short life. In illustration, a few of the more important reactions of free radicals will be given.

In the gaseous phase free radicals collide and combine. We have already seen that two methyl radicals unite to give the stable ethane molecule; a methyl and ethyl radical to give propane; and so on. In solution, however, such changes are much less common since the free radicals combine immediately with the surrounding solvent molecules. For instance, the photodecomposition of methyl ethyl ketone in a hydrocarbon (RH) solvent proceeds by the following mechanism.



This interaction of free radicals with solvents is used to diagnose the presence of free radicals in solution. Sometimes the free radicals combine not with hydrogen but with halogen atoms. The phenyl radical, for instance, attacks methyl bromide to form bromobenzene.

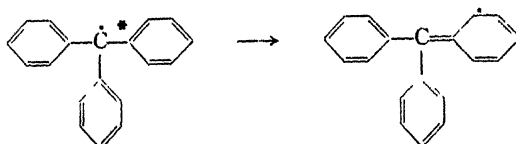
(3) *Magnetic susceptibility measurements* have proved of great service in the detection and investigation of free radicals. Most organic molecules contain only co-valent bonds and each of these bonds consists of two electrons of opposite spin. Such compensated electron pairs give rise to no magnetic field and the molecules are therefore *diamagnetic*. In free radicals, on the other hand, there is in addition to the covalent linkages

MECHANISM OF REACTIONS

a single non-compensated electron giving rise to a magnetic field. Free radicals are therefore highly *paramagnetic*, and this property is frequently used in free radical research.

The stability of free radicals varies greatly. The methyl radical, obtained by passing lead tetramethyl in hydrogen through a tube heated to 600-800° is detected by attacking a lead mirror, and has a half-life period of 6×10^{-8} seconds at a pressure of 2 mm. In general, simple radicals have a short life. More complex molecules, however, may be stabilised and have a life period of years. Mesomerism, for example, explains the stability of the radical triphenylmethyl.

This is regarded as a hybrid of $(C_6H_5)_3C\cdot$ and of six equivalent structures in which the odd electron from the central carbon atom is distributed over the six available ortho positions and stabilised by resonance. The change may be supposed to occur by a separation of the two electrons constituting one link of a 1 : 2-double bond (marked *),



followed by union of one of them with the odd electron on the central carbon. The other electron is retained on the ortho carbon atom of the ring. In the simple radical methyl, $CH_3\cdot$, the possibility of such a stabilising resonance does not exist and the structure is highly unstable.

NOMENCLATURE OF ORGANIC COMPOUNDS

In organic chemistry one and the same compound is frequently described with equal accuracy in a number of ways, an author employing different names as he desires to lay emphasis on the properties of the compound or on its relationship to some other substance. For the latter reason many animal and vegetable products have been named in reference to their origin, *e.g.* urea, uric acid, malic acid (from apples) and citric acid. Owing to the rapid development of this branch of science the need for a standard system of nomenclature was realised at an early stage. The position of things in 1892 was such that an international commission was called to meet in Geneva, for the purpose of deciding upon a system of nomenclature by which the constitution of an organic compound could be simply and clearly expressed. This task was only partly completed, but the findings of the Geneva commission have been frequently used, more particularly in describing compounds of the fatty series.

In general, organic compounds may be referred back to one or another of a limited number of parent or index substances, from which they may be considered to be derived by replacement of hydrogen with

other atoms or groups. Modern nomenclature is built up from the names of these parent compounds by the addition of certain endings, some of which are given below.

Saturated hydrocarbons.	Alkanes	<i>ane</i>
Ethylenic hydrocarbons.	Alkenes	<i>ene</i>
Acetylenic hydrocarbons.	Alkynes	<i>yne</i>
Alcohols, phenols .		<i>ol</i>
Aldehydes . . .		<i>al</i>
Ketones		<i>one</i>
Nitrogenous bases		<i>ine</i>

Thus ethyl alcohol is ethanol and propenol is allyl alcohol. Most of the other substituent groups are indicated in the usual manner by prefixes. In the case of compounds possessing several characteristic groups, these are named in a certain agreed sequence, and two or more of the same groups, if present in a compound, are indicated by the prefixes di-, tri- and so on. The respective positions of the substituents are shown by lettering or numbering.

Full details of modern organic nomenclature can be obtained in the references given in the footnote.¹

¹ *British Chemical Nomenclature* by A. D. Mitchell (Arnold and Co., 1948). *Editorial Reports on Nomenclature, J.*, 1952. 5057.

The Aliphatic or Fatty Compounds

THE numerous compounds classified under this title may be regarded as derived from the hydrocarbon methane, CH_4 , and are therefore termed methane derivatives. Since the common animal and vegetable fats similarly fall under this heading, the whole series is frequently known as the aliphatic or fatty series. Structurally, compounds of this type are distinguished by containing open carbon chains in contrast to the closed chains or rings of the aromatic or benzene series.

Organic research, which for many years had been pursued for the most part among aromatic compounds, has recently turned towards the investigation of aliphatic derivatives. New sources have been discovered for the preparation of aliphatic substances, and the growing interest in biochemistry has given rise to more and more work in this branch, since the chief reactions of plant and animal life are of an aliphatic nature.

I

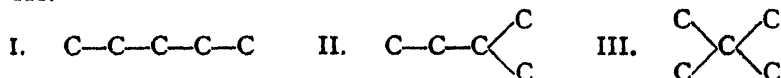
Hydrocarbons

I.—SATURATED HYDROCARBONS OR PARAFFINS.



Nomenclature.—The homologous series of hydrocarbons possessing the general formula $\text{C}_n\text{H}_{2n+2}$ is termed "saturated," in contradistinction to the ethylene series which exhibits pronounced additive or unsaturated properties. Not only are these compounds incapable of uniting directly with hydrogen, for example, but they are also extraordinarily resistant to attack by the majority of reagents, such as strong bases and acids, a peculiarity which has led to them being known as the paraffin series (*parum affinis*: little affinity). The names of the individual members are derived from the Greek numerals indicating the number of carbon atoms in the molecule, by the addition of the syllable -ane, *e.g.* hexane, C_6H_{14} ; heptane, C_7H_{16} ; octane, C_8H_{18} , and so on. Only the first four members have special names, viz., methane, CH_4 ; ethane, C_2H_6 ; propane, C_3H_8 ; butane, C_4H_{10} .

As already mentioned, the fourth member of the series exists in two forms, butane and isobutane, and these may give rise to different pentanes according as the carbon chain is straight as in I, or branched as in II and III.¹



When a carbon atom is combined in such a manner that only one of its four valencies is satisfied by carbon, it is termed a **primary carbon atom**; similarly, if two, three or all four valencies are linked to carbon, the atom under consideration is termed **secondary**, **tertiary** or **quaternary** respectively. Methane, with four valencies linked to hydrogen, is an exceptional case.

Those hydrocarbons with straight carbon chains are known as *normal* hydrocarbons in distinction to the *iso*-hydrocarbons containing branched chains.

Since other compounds of the fatty series may be derived from the paraffins by replacement of one or more hydrogen atoms by other elements or groups, it has in some cases been found convenient to coin special names for the hydrocarbon residues or radicals which remain after removal of such hydrogen atoms.

Monovalent radicals, of the general formula $\text{C}_n\text{H}_{2n+1}$, which result from the paraffins by the removal of one hydrogen atom, are known under the general name of *alkyl* (or *aliphyl*) groups. The name of each individual group is obtained from that of the corresponding saturated hydrocarbon by changing the end syllable -ane into -yl, *e.g.* *methyl*, CH_3- ; *ethyl*, C_2H_5- ; *propyl*, C_3H_7- . For reasons which will be seen later (p. 159) the group C_5H_{11} , instead of being called *pentyl*, is known as the *amyl* group.

Ethyl and **methyl** have been shown to exist in the free state, but even at low temperatures they polymerise rapidly. These radicals are liberated when the corresponding lead compounds, such as lead tetraethyl, PbEt_4 , or lead tetramethyl, PbMe_4 , are heated.

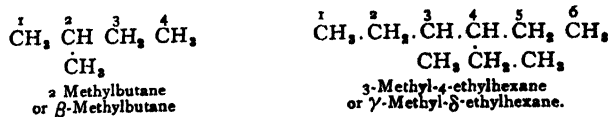
The **divalent radicals** resulting from the saturated hydrocarbons by removal of two atoms of hydrogen have the general formula C_nH_{2n} , and are named after the parent hydrocarbon by changing the end syllable -ane into -ylene, *e.g.* *methylene*, $\text{CH}_2=$; *ethylene*, $\text{C}_2\text{H}_4=$; *propylene*, $\text{C}_3\text{H}_6=$.

Similarly, the **trivalent radicals** of the general formula $\text{C}_n\text{H}_{2n-1}$ are written with the termination -ine; *methine*, $\text{CH}\equiv$; *ethine*, $\text{C}_2\text{H}_3\equiv$; *propine*, $\text{C}_3\text{H}_5\equiv$.

According to the Geneva proposals the names of the more complex saturated hydrocarbons are derived in the following manner. The names given above are retained

¹ The number of isomerides rises with surprising rapidity as the number of carbon atoms in the chain increases. There are five hexanes, nine heptanes and eighteen octanes theoretically possible.

for those hydrocarbons of normal straight chain constitution. The iso-hydrocarbons, containing branched chains, are regarded as alkyl substitution products of the longest straight chain hydrocarbon which it is possible to assume from the formula. In dealing with the higher members, the carbon atoms of the longest chain are numbered from one end, by which means the position of the substituting alkyl groups may be indicated. The numbering starts at that end of the carbon chain which is nearest the substituting groups. In the case where two side chains are attached to a pair of carbon atoms symmetrically situated in the main chain, the numbering commences at the end nearer the simpler side chain. In this way we obtain the following, modified to English and American practice (see also p. 100):



Occurrence and General Properties.—The homologous series of the paraffins has been investigated with few omissions from the first member methane, CH_4 , to the thirty-fifth member, pentatriacontane, $\text{C}_{35}\text{H}_{72}$. After the latter, the highest known member is heptacontane, $\text{C}_{70}\text{H}_{142}$. The first four members of the series are gases under normal conditions, then follow liquids, and from $\text{C}_{18}\text{H}_{38}$ upwards they are solids at the ordinary temperature. As already mentioned, these compounds are very stable towards chemical reagents, even resisting the action of concentrated sulphuric or fuming nitric acid, though nitration in the gaseous phase readily occurs (see p. 171). On the other hand, chlorine and bromine interact with comparative ease to form substitution products, from which other derivatives are readily obtainable. The boiling-points of the paraffins rise with increase of molecular weight; among the lower members a difference of CH_2 corresponds to an increase of about 30° , the amount becoming smaller as the series is ascended.

Immense quantities of saturated hydrocarbons are found free in nature as *petroleum*, or *mineral oil*, the American variety of which consists almost exclusively of paraffins, and is a mixture of many members of the series from the lowest to the highest. *Ozokerite* or *earth-wax*, found in Galicia, is a mixture of the solid members, and products rich in paraffins are also obtained on the industrial scale by the distillation of fats and brown coal.

Until recently the dry distillation of coal was chiefly carried out in such a way that the aliphatic decomposition products first formed were, for the most part, converted into compounds of an aromatic nature (coal tar) by subsequent contact with the glowing walls of the retort. It has been shown, however, by the work of Börnstein, Pictet, Wheeler and Franz Fischer, that in the distillation of coal by the *low temperature carbonisation process*, or under reduced pressure, the primary distillate is composed mainly of aliphatic compounds. By employing such a process on the large scale it is now possible to obtain from coal all the products characteristic of the petroleum industry. Tars of aliphatic nature are also prepared by heating coal or ordinary coal tar with hydrogen

nder high pressure, and by the hydrogenation of carbon monoxide in the presence of very highly active nickel and cobalt catalysts (see also . 117).

Methane, marsh gas, CH_4 . *Occurrence.*—From many places in the earth's surface an issue of *natural gas* occurs, consisting of methane and other homologues of the paraffin series, together with a little admixed carbon dioxide and nitrogen. At Baku, for example, the burning gas constitutes the "holy fires of Baku," and attracted the attention of the re-worshippers as early as 600 A.D.

Natural gas is found in large quantities in most oil fields, and in America was formerly harnessed for lighting and the production of power, but now is used to prepare motor spirit. Natural gas sometimes consists mainly of methane and ethane and is described as "dry," but frequently appreciable amounts of propane and butane are also present, the gas then being known as "wet" gas on account of the separation of liquid propane and butane on cooling under pressure. Nearly 10 per cent. of American gasoline (petrol) comes from "wet" natural gas. From 1,000,000 cubic feet of natural gas as much as 2500 gallons of *natural gasoline* may be obtained.

Methane issues from the seams of coal-mines, where by diffusing into the atmospheric air it forms an explosive mixture (fire-damp).

Natural gas is now an important raw product for the preparation of chemicals such as formaldehyde, methyl alcohol, acetylene, etc.

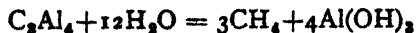
Methane is produced in considerable quantities, and in a comparatively pure state, by the putrefaction of organic matter and the fermentation of cellulose under stagnant water; hence the name of marsh gas. For similar reasons (reductive fermentation of cellulose and decomposition of proteins) it is present in the intestinal gases, especially of herbivorous animals. In addition, it forms one of the chief components of coal gas and is found in the gases from cracked petroleum.

Preparation.—Methane is obtained by the following methods :—

1. In the laboratory it is prepared by heating a mixture of sodium acetate and soda-lime. The active constituent of soda-lime in this reaction is sodium hydroxide, but the pure alkali is not used owing to its corrosive influence on the glass of the containing vessel.



2. Another laboratory method is to boil aluminium carbide with water :



3. By the reduction of methyl iodide with nascent hydrogen, *e.g.* by means of alcohol and the aluminium-mercury couple, or zinc and hydrochloric acid.

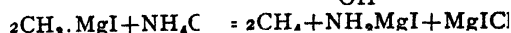
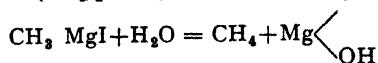
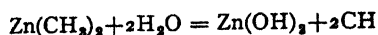


The following methods are of importance from the theoretical rather than the practical standpoint.

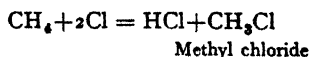
4. Methane is produced together with ethylene and acetylene by the combination of carbon and hydrogen in the electric arc, $C+4H=CH_4$. This reaction deserves mention since it provides a method of synthesising methane from its elements.

By the *complete synthesis* of an organic compound is meant formation from its constituent elements, or from such simpler compounds as have already been synthesised from their elements.

5. Methane is also formed by the decomposition of zinc methyl, $Zn(CH_3)_2$, or more conveniently of methyl magnesium iodide, with water. Methyl magnesium iodide also interacts with ammonium chloride to give methane.



Properties of Methane.—Methane is a colourless and odourless gas, boiling at -164° . At still lower temperatures it solidifies to crystalline mass of melting-point -186° . Methane is combustible, burning with a slightly luminous flame to form carbon dioxide and water ($CH_4 + 2O_2 = CO_2 + 2H_2O$). When mixed with air or oxygen and ignited, methane explodes violently; dangerous mixtures of this type occur in coal-mines as fire-damp. Chlorine has no action on methane in the dark, but in diffused daylight chlorine-substituted derivatives are formed, *e.g.*—

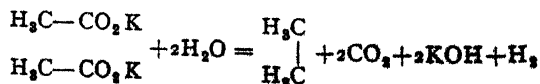


As will be seen later, these substitution products may be utilised for the conversion of methane into other compounds.

Formaldehyde is manufactured in the U.S.A. by oxidation of methane

Ethane, $H_3C \cdot CH_3$, is found dissolved in petroleum, and escape from the earth's surface in many places (*e.g.* North America). It is also a constituent of "cracked" petroleum.

It may be prepared by the general methods given above. From a theoretical point of view, the discovery of Kolbe in 1848, that ethane was formed by electrolysis of a concentrated solution of potassium acetate is of great importance. The discharged acetanions at the anode interact with one another under the experimental conditions to give ethane and carbon dioxide. At the cathode the discharged potassium ions react with water to form hydrogen and potassium hydroxide.

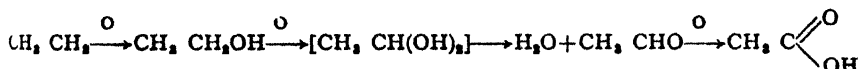


This is the first and most typical of those synthetic reactions which organic chemistry owes to electrolysis. Wurtz carried the process a step further by electrolysing a mixture of the salts of two fatty acids, and so by the combination of two different electrolytic residues synthesised higher hydrocarbons.

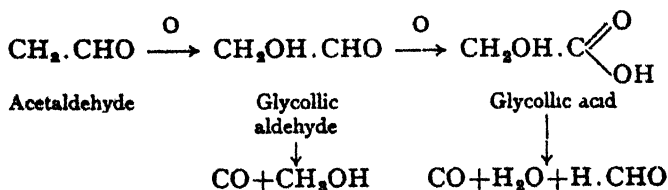
Ethane is a colourless, odourless gas, which burns in air with a feebly luminous flame; its critical temperature is $+34^{\circ}$ and critical pressure 50 atmospheres. It is very little soluble in water but more so in alcohol. Chlorine and bromine readily react with it to give substitution products, as does nitric acid in the vapour state.

Propane, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_3$, is obtained in almost unlimited quantities in the U.S.A. from natural gas or petroleum. It is sometimes used instead of acetylene for cutting steel-plate.

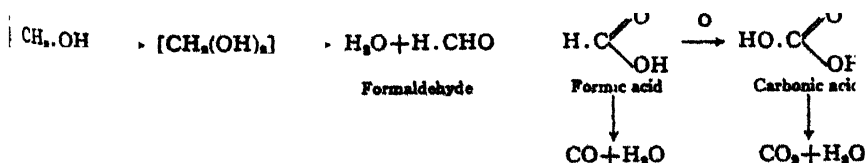
Slow Combustion of Hydrocarbons.—An extended investigation of "slow combustion" of methane and ethane when heated with oxygen high pressure and relatively low temperatures has been carried out by W. A. Bone and his co-workers.¹ The results show that under these conditions oxidation proceeds by successive stages of hydroxylation ($\rightarrow \text{OH}$). Thus with a mixture of ethane (9 mols.) and oxygen (mol.) at 273° and under 100 atmospheres pressure, it was found possible to follow quantitatively the conversion of ethane into carbon dioxide, the intermediate products such as ethyl alcohol, acetaldehyde and acetic acid being identified and estimated. The main stages of the reaction are summarised below.



Acetaldehyde is assumed to undergo further hydroxylation to form glycollic aldehyde and glycollic acid, each of which may decompose at the temperature of reaction to yield simpler products.



Finally, by a continuation of the same process, methyl alcohol and formaldehyde are oxidised to carbon dioxide.



¹ W. A. Bone, *J.*, 1933, 1601; D. M. Newitt and A. E. Haffner, *Proc. Roy. Soc.*, 1932, A, 591; Newitt and Bloch, *ibid.*, 1933, A, 240, 426.

There is reason to believe that this mechanism of hydroxylation is also operative in a number of other types of oxidative reactions.

Higher Homologues of Methane

Some of the higher homologues of the paraffin series—propane and butane—occur in natural gas, and many are obtained on the large scale by the “cracking” of petroleum (see p. 113). For their preparation, modifications of the methods 3 and 5 given on pp. 105, 106 may be employed. The best general method is perhaps the decomposition of alkyl magnesium halides with aqueous ammonium chloride, which yields the hydrocarbons directly in the pure state. In addition, the following special methods are available :—

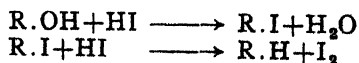
(a) *Synthesis from lower halogenated derivatives* by treatment with metallic sodium (*Wurtz* reaction), zinc (*Frankland*) or finely divided silver. Unsaturated hydrocarbons of the ethylene group are often formed at the same time.



These reactions proceed most readily with the iodo-derivatives and occur through the intermediate formation of metallic alkyls or of the unstable free alkyl radicals.

(b) *From unsaturated hydrocarbons*, by passing them in the gaseous state mixed with hydrogen over a suitable heated catalyst such as finely divided nickel, platinum or palladium. The two last named catalysts will also bring about hydrogenation at ordinary temperatures. For further details see p. 122.

(c) *Reduction of alcohols, aldehydes, ketones and carboxylic acids*, by heating with hydriodic acid and red phosphorus. In this manner alcohols are first converted into the corresponding iodides, which then react with more hydriodic acid and are reduced to hydrocarbons. The iodine so liberated combines with the red phosphorus to form PI_3 and this reacts with water produced in the first stage to regenerate more hydriodic acid.



Mineral Oil, Petroleum¹

Occurrence and Formation.—Petroleum is found in many places, of which the most important, from an industrial point of view, are Oklahoma and Pennsylvania in North America, the region in Caucasia having Baku as its centre, and Iran. In addition, it occurs on a considerably smaller scale in Galicia, Roumania, Hungary and numerous other parts. From these sources the great petroleum industry of to-day has been built, and the world's production of petroleum is now some 250,000,000 tons a year.

¹ “Chemistry and the Petroleum Industry,” by A. E. Dunstan, *Royal Institute of Chemistry*, 1942.

There is still great doubt as to the origin of petroleum. Recently, Treibs¹ has isolated from various samples of petroleum a number of porphyrins, some of which are related to chlorophyll and others to haemin. It is therefore concluded that both plant and animal remains play a major part in the formation of petroleum deposits, and this organic source is further indicated by the presence of optically active compounds and of quinoline derivatives. The present view is that these microscopic organic remains were deposited as ooze on the beds of swamps and seas in primeval times. Further successive layers formed throughout the ages sealed them from contact with air and incorporated them in the earth's crust, where they were subjected to intense pressure and probably to an appreciable rise in temperature. Under these conditions the fossil remains decomposed, the proteins, carbohydrates and to a lesser extent the fats gradually breaking down to form petroleum. The oil tapped by the mining engineer is usually a large accumulation which has collected between the grains of an underground sand bed or more rarely in the cracks of limestone rock.

Composition.—Petroleum consists of a mixture of gaseous, liquid, and solid hydrocarbons whose composition varies with the place of origin. These hydrocarbons are members of the paraffin series, olefins, cycloparaffins or naphthenes, and aromatic compounds. No two sources give exactly the same type of oil. *Pennsylvanian oil* consists chiefly of paraffins, and *Caucasian oil* contains about 80 per cent. of *naphthenes* such as cyclohexane along with smaller quantities of aromatic compounds (benzene, etc.). The Galician oilfields yield petroleum with a good percentage of both naphthenes and paraffins, while other oils such as that from Borneo contain considerable amounts of toluene and other aromatics.

Constituents of Petroleum

The gaseous component of petroleum—natural gas (p. 105)—is mainly methane with smaller quantities of ethane, propane, butanes, and pentanes. "Dry" gas consists chiefly of methane and ethane and cannot be liquefied under ordinary conditions of temperature and pressure; "wet" gas contains considerable quantities of the higher homologues—propanes and butanes—which condense when the gas is cooled under pressure. The analysis of figures for two gases—one "wet" and one "dry"—are given.

	CH ₄	C ₂ H ₆	C ₃ H ₈	C ₄ H ₁₀
"Dry" gas	85%	9%	3%	1%
"Wet" gas	42%	28%	18%	5%

Further quantities of the above gases are obtained by "stabilising" the crude oil by distillation under pressure.

It is perhaps unfortunate that the main gaseous product is methane, an intractable hydrocarbon which until recently was used mainly as a fuel in industrial areas and for the manufacture of *carbon black*, great quantities of which are required for the rubber industry. On pyrolysis methane yields acetylene, and it is anticipated that increasing quantities

¹ A. Treibs, *Ann.*, 1934, 509, 103; 520, 42; 1935, 527, 172; 520, 144.

of this important unsaturated and reactive hydrocarbon will be obtained in this way on the industrial scale.

The higher homologues, propane and butanes, are easily liquefied under moderate pressure and are sold in cylinders under various names such as calorgas for heating purposes.

Petroleum Distillation Products.—In the early days of the petroleum industry the main product sought was illuminating oil; but, with the advent of the internal combustion engine, petroleum is now worked up to give the maximum amount of *gasoline* (known as *petrol* in this country) and, to a lesser extent, *lubricating oil*. These are, as stated above, mixtures of hydrocarbons, but in recent years petroleum has also been used to prepare pure organic chemicals, and this is being developed on an ever-increasing scale.

The following table (page 111) gives a list of the main products of petroleum distillation.

In practice fractions or cuts are made to conform to industrial needs and specifications. Lighter fractions are frequently sold as petrol ether boiling over a range of twenty degrees (40° to 60°, 60° to 80°, 80° to 100°, and 100° to 120°) and are used as solvents. The fraction boiling between 90° to 120° is sometimes known as *ligroin*.

At the other end of the scale, lubricating oil is of great value for machinery. Unlike the fatty acids, which decompose in the course of time and then attack metals, the petroleum oils have the advantage of being stable in air. They contain, however, undesirable ingredients such as aromatic and unsaturated compounds which were formerly removed by agitation with sulphuric acid. Lubricating oil refined in this way is not entirely suitable for the modern automobile and aircraft engine, and the undesirable constituents are now removed by *selective solvation*, whereby the crude lubricating oil is treated with a suitable solvent which extracts the impurities. Hundreds of solvents have been tried: among the more successful may be mentioned β : β' -dichlorodiethyl ether, nitrobenzene, furfural, liquid sulphur dioxide, propane, etc. The purified mineral oils are frequently blended with vegetable oils such as lard, coconut or castor oil, etc., to increase their "oiliness."

Vaseline or petroleum jelly is used for many purposes—pomades, salves, etc. **Paraffin wax** is a valuable by-product and is composed of solid hydrocarbons, mostly of the paraffin series. It is also obtained from the distillation of peat, lignite, shale, etc. In the paraffin industry in Scotland bituminous shale is largely used for this purpose, and in Germany deposits of brown coal are utilised. Paraffin waxes with suitable melting-points are employed either alone or admixed with higher fatty acids in the manufacture of candles. Softer varieties are used in the match industry.

Fuel from Petroleum

Fuel oil is used as a fuel in ships and to a certain extent in locomotives. Kerosine is used as an engine fuel only to a limited extent, but with the

development of jet propulsion there is every possibility that a fuel of the kerosene type will be used in enormous quantities in the future. Kerosine is purified by the addition of strong sulphuric acid and agitation with compressed air. After the removal of the tarry products and sulphuric acid layer, the kerosine is filtered through Fuller's earth or bauxite and is obtained as a water-white liquid. The product so obtained is used for heating and lighting and is known in this country as *paraffin oil*.

Products from Crude Petroleum

<p>CRUDE OIL ↓</p>				
Natural Gas	Methane, etc.	Calorgas	Casinghead petrol	Carbon Black
Gasoline Fraction (b.p. 40°-205°)	Aviation spirit	Motor spirit	Petrol ether	White spirit
Kerosine Fraction (b.p. 175°-325°)	Paraffin for tractors, etc.	Paraffin for lighting and heating		Signal lamp oil
Fuel Oil Fraction (b.p. above 275°)	Gas oil	Diesel oil		Furnace oil
Lubricating Oil Fraction	Medicinal oil	Transformer oil	Motor oil	Grease
Wax Fraction	Petroleum jelly	Paraffin wax (matches)		Paraffin wax (candles)
Asphalt Fraction	Road spraying asphalt	Stone coating asphalt		Petroleum coke

Many risks are attached to the use of insufficiently purified oil for lighting and fuel purposes, particularly if lower-boiling constituents are present. In order to decide whether an oil may be safely used its *flash-point* is determined by warming the oil in a special apparatus and finding by experiment the temperature at which the vapour above the liquid is inflammable. The lowest flash-point permissible in Great Britain is 73° F.

The main petroleum product in demand is, of course, motor and aviation spirit. This demand is so enormous that it cannot be met by the supply of straight-run gasoline (petrol) and methods have therefore been introduced whereby fractions hitherto regarded as of little value are converted into motor fuel. The gasoline supply now comes mainly from the "**cracking**" of higher petroleum fractions and the "**reforming**" of

straight-run gasoline (see below). Such processes are specially necessary at this time with its urgent demand for aviation spirit of high *octane number*.

Knock. Octane Numbers. Theoretically the efficiency of an internal combustion engine is directly proportional to the compression ratio but in practice this is found to hold only up to a certain limit. Increase of the compression ratio above a certain point invariably results in "knocking" and decrease in power. Since the maximum compression ratio attained by any given engine without knocking is found to depend to a considerable extent on the nature of the fuel used, it is a matter of importance to determine the "anti-knock" value of fuels and to this end octane numbers were introduced in 1929. *n*-Heptane and *iso*-octane (2:2:4-trimethylpentane) are taken as standards, the former being rated as zero and the latter as 100. The rating of a fuel is expressed in terms of the octane number, *i.e.* the percentage by volume of *iso*-octane in a mixture of *iso*-octane and *n*-heptane which has the same tendency to knock under the same conditions as the fuel under test. The standard engine used was introduced by the Co-operative Fuel Research Committee of the Society of Automotive Engineers, and octane numbers of internal combustion engine fuels are almost universally determined by the *C.F.R. Method*.

It is not difficult to realise the significance of fuel of high octane number. The higher the octane number the higher is the compression ratio which can be attained without knocking and the greater is the power and efficiency of a given engine. For example ¹ :—

Octane Number	Maximum Power.	Fuel Consumption c.c./h.p./hour.
100	777	230
87	679	274
84	659	291
73	600	325

It has been found that the normal straight-chain paraffins are the worst fuels for producing "knocking" and that unsaturated compounds and aromatic compounds have the best "anti-knock" properties. Generally speaking, the more "compact" the molecule the greater is the "anti-knock" efficiency, and the longer the main carbon chain the lower is the "anti-knock" efficiency. These points are shown by the following table (page 113) in which only the skeletal structures are given, hydrogen atoms being omitted.

By the addition of small quantities of an anti-knock compound the octane number can be further raised, and values well above 100 are now obtained. Lead tetraethyl, b.p. 200° C., is by far the most commonly used of these "anti-knock" compounds, and is employed with ethylene dibromide in order that the lead may be eliminated as lead bromide.

Cetane number.—Octane numbers are applicable only to fuels used in "sparkling" engines. For Diesel engines a somewhat similar standard

¹ Quoted from Eric S. Gyngell, *Applied Chemistry for Engineers*, p. 127

known as the cetane number is employed. Diesel fuel is matched against a mixture of *cetane* (a saturated hydrocarbon, $C_{18}H_{38}$) and α -methyl-naphthalene. The percentage of cetane in the blend which has the same ignition lag as a given fuel is known as the cetane number of that fuel.

<i>Octane Numbers and Chemical Constitution</i>		
<i>Normal paraffins</i>		
$-C-C-C-$	100+	
$-C-C-C-C-$	95	
$-C-C-C-C-C-$	58	
$-C-C-C-C-C-C-$	34	
$C-C-C-C-C-C-C-$	0	
<i>Olefins</i>		
$-C-C-C-C-C=C-$	80	
$-C-C-C-C=C-C-$	89	
$C-C-C-C-C-C=C-$	54	
$C-C-C-C-C=C-C-$	84	
<i>Isomeric heptanes</i>		
$\begin{array}{c} C \quad C \\ \quad \\ -C-C-C-C- \\ \\ C \end{array}$	116	
$\begin{array}{c} C \\ \\ -C-C-C-C-C- \\ \\ C \end{array}$	98	
$\begin{array}{c} C \quad C \\ \quad \\ -C-C-C-C-C- \\ \quad \\ C \quad C \end{array}$	80	
<i>Cyclic compounds</i>		
$\begin{array}{c} C \quad C \\ \diagdown \quad \diagup \\ C \quad C \\ \diagup \quad \diagdown \\ C \quad C \end{array}$	80	
$\begin{array}{c} C \quad C \\ \diagdown \quad \diagup \\ C=C \\ \diagup \quad \diagdown \\ C \quad C \end{array}$	100+	

Cracking Processes.—The higher petroleum fractions may be broken down into lower-boiling fractions by *controlled pyrolysis* or "*cracking*," the conditions employed resulting in the bigger molecules being broken down into molecules of smaller molecular weight. The process may be carried out in the vapour or liquid phase, with or without catalysts. The temperatures vary considerably, but generally lie between 400° and 700° . Liquid phase cracking is worked under pressures between 150 and 1300 lb./sq. in. Vapour phase cracking is usually under a small pressure of less than 50 lb./sq. in.; unlike the previous method it cannot be applied to high fractions such as fuel oils.

As the following table shows, cracked gasoline has a higher content of olefinic and aromatic compounds and is therefore a better fuel with a higher octane number than straight-distilled gasoline. Cracked gasoline is often blended with inferior gasoline.

<i>Comparison of Straight-run and Cracked Gasoline</i>		
Percentage of	Straight-run	Cracked
Unsaturated	1.4	10.9
Aromatics	4.9	19.8
Naphthenes	23.7	18.0
Paraffins	69.8	51.3

In recent years catalytic cracking has been developed greatly, good yields being obtained on account of the comparative mildness ($500^{\circ}\text{C./30 lb./sq. in.}$) of the conditions employed. The *Houdry Process*, which cracks gas-oil with hydrated aluminium silicate as catalyst, gives gasoline with an octane number of about 80. An extremely important development is the successful application of a moving catalyst. In the *Thermoform Process*¹ the catalyst falls through the vaporised reactants at a temperature of between 450° and 500° . It is obvious that under such conditions extremely efficient contact between reactants and catalysts can be effected, and further, by including a regenerating unit in the system the poisoned catalyst can be revived without interruption.

Cracking is an extremely complex process, the thermal breakdown of larger molecules to smaller molecules being accompanied by other changes such as polymerisation, isomerisation, etc. (see below). When straight-run gasoline undergoes pyrolysis the most important change is the isomerisation of the straight-chain paraffins to branched-chain paraffins. This treatment to increase the octane number of gasoline is known as **reforming**, and is a cracking process carried out under high pressure for twenty seconds. Great quantities of gasoline are now reformed.

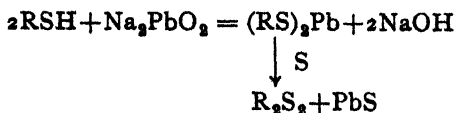
Among the products of cracking is **cracked gas**, which consists of a mixture of saturated and unsaturated hydrocarbons and some hydrogen. This now forms an additional source of gasoline. By heating under pressure with or without catalysts considerable quantities of gasoline are produced. Straight-run and cracked gasoline must be further refined owing to the presence of evil-smelling sulphur compounds and unstable constituents such as polyolefins which tend to polymerise and form "gums." Among the methods of purification are the following :—

- (1) Treatment with sulphuric acid ;
- (2) Treatment with sodium plumbite solution ;
- (3) Treatment with sodium hypochlorite ;
- (4) Preferential adsorption.

Sulphuric acid refining was formerly the most widely used method. but it suffers from the disadvantage that it decreases the octane number by two or three units and is accompanied by considerable losses. Polyolefins are polymerised by sulphuric acid to tars which can be readily removed, and the acid also helps to remove sulphur compounds such as mercaptans. The latter are also removed from "sour" gasoline by "sweetening" with sodium plumbite or sodium hypochlorite. Sodium plumbite converts mercaptans to lead mercaptide, which with sulphur

¹ T. J. Van Antwerpen, *Ind. Eng. Chem.*, 1944, 36, 694.

gives disulphides with no unpleasant smell. Sodium hypochlorite oxidises hydrogen

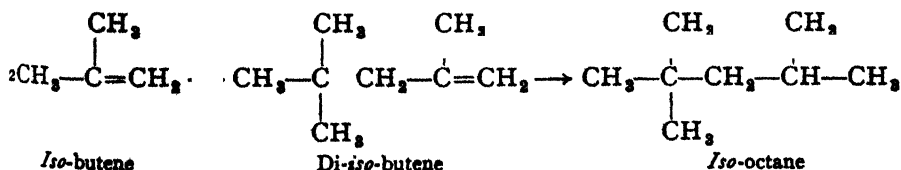


sulphide to sulphur and the mercaptides to disulphides and sulphuric acid.

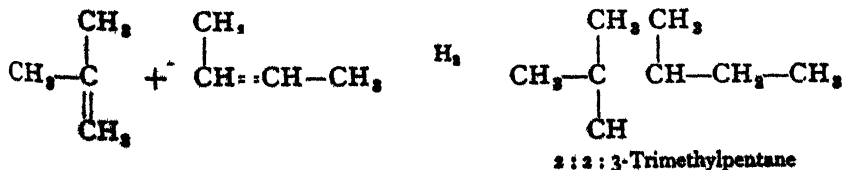
Cracked gases require further treatment to prevent oxidation and consequent gum formation on standing. For this purpose anti-oxidants or inhibitors—mostly phenols such as *p*-benzylaminophenol, cresols, hydroquinone, catechol, etc.—are added to gasoline in small quantities.

Chemistry of the Cracking Process.—It has already been emphasised that the chemistry of the cracking process is very complicated and involves not only molecular disintegration but also polymerisation, alkylation, cyclisation, aromatisation, etc. A few examples of the more important of these processes is given below.

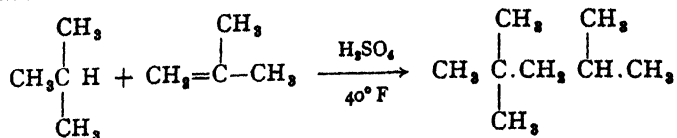
Polymerisation.—A variety of saturated and unsaturated hydrocarbons is obtained by the cracking process, among them *n*-butane and *iso*-butane, *n*-butenes and *iso*-butene. It is from these that components of modern high-grade aviation spirit such as *iso*-octane (2 : 2 : 4-trimethylpentane) and *neohexane* (2 : 2-dimethylbutane) have been manufactured. Gasoline with good anti-knock properties results from the polymerisation of the butenes and *iso*-butenes either by the use of high temperatures and pressures or under milder conditions with catalysts (*e.g.* phosphoric acid). The "feed" sometimes consists of a mixture of butanes and butenes, the saturated hydrocarbons being converted into the unsaturated butenes in the process. Polymerisation of the butenes results in formation of *iso*-octenes which are then hydrogenated to *iso*-octanes, and the process is now used to prepare practically pure *iso*-octane by controlling conditions so that *iso*-butene of good quality is fed into the plant.



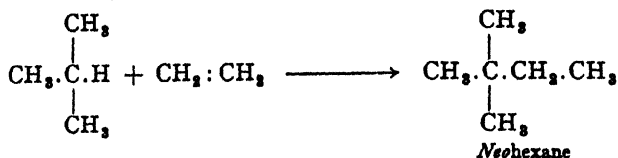
Another example is the co-polymerisation of *iso*-butene and *n*-butene followed by hydrogenation when 2 : 2 : 3-trimethylpentane is obtained.



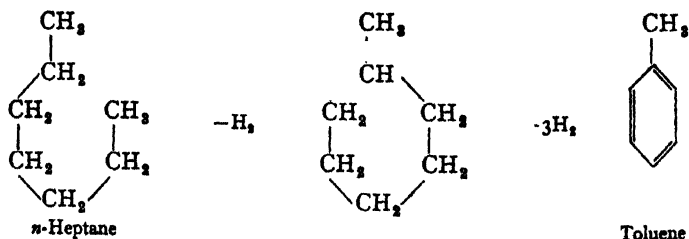
A very elegant process in which a paraffin is alkylated by means of an olefin is that of thermal or catalytic alkylation¹ or alkanation. For example, *iso*-octane is obtained in one operation by the combination of *iso*-butane and *iso*-butene.



Neohexane, 2:2-dimethyl-*n*-butane, a fuel with a high octane number and excellent lead tetraethyl susceptibility is prepared in like fashion from *iso*-butane and ethylene at high temperatures and pressures.



Another method is **aromatisation**² in which aliphatic compounds undergo cyclisation and dehydrogenation to form aromatic compounds. Good yields are obtained by this process when aliphatic compounds containing six or more carbon atoms are ring-closed. For example, toluene is obtained in 75 per cent. yield from *n*-heptane.



A form of aromatisation is that termed **hydroforming** in which heavy naphthas are treated with catalysts such as molybdenum trioxide on alumina in presence of hydrogen. Hydrogen is used in this process to repress the formation of coke and olefins. Various fractions result from which toluene, xylenes, etc., can be isolated.

The Petroleum Chemical Industry

A recent development of the petroleum industry is the production of large quantities of alcohols, ketones, etc. Indeed, the large-scale preparation of organic chemicals directly or indirectly from petroleum and natural gas is probably the most outstanding development of industrial

¹ M. E. Clark, *Chem. Met. Eng.*, 1940, 47, 225; Gustav Egloff, W. H. Hubner, P. M. Van Arndell, *Chem. Rev.*, 1938, 22, 175. ² A. V. Grosse, J. C. Morrell, and J. Mattose, *Ind. Eng. Chem.*, 1940, 32, 528; H. G. M. Fischer and A. B. Welky, Jr., *Chem. Met. Eng.*, 1944, 52, 92.

chemistry since the discovery of coal tar as a rich source of aromatic compounds. To-day some 175 organic chemicals are obtained from petroleum and the number is continually increasing.

From the cracking and reforming of petroleum great volumes of gas are produced annually—350,000,000 cubic feet in the United States. Among these gases are methane, ethylene, propylene, the butenes, etc., and from these a large number of important chemicals are obtained, some of which are shown in the following table :—

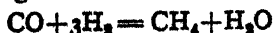
Some Chemicals manufactured from Petroleum and Natural Gas

Methane	{	Methyl chloride	→ Methylene chloride	→ Chloroform
		Formaldehyde	→ Methyl alcohol	
		Formamide	→ Hydrocyanic acid	
Ethylene	{	Ethyl alcohol	→ Butadiene	
		Ethylbenzene	→ Styrene	
		Ethylene chlorhydrin	→ Glycol, etc.	
Propylene	{	Allyl chloride	→ Allyl alcohol	→ Glycerol
		Isopropyl alcohol	→ Acetone	→ Methyl methacrylate
			↓ Dibutene	→ Acetic anhydride
Propane	{	Nitromethane		
		Nitroethane		
		Nitropropanes		
Butylene	{	Butyl alcohols		
		Butadiene		
Amylenes	—	Amyl alcohols		
n-Hexane	—	Benzene		
Heptane	—	Toluene		

Low Temperature Distillation of Coal.—It has already been mentioned that by varying the conditions under which the dry distillation of coal is conducted we may obtain tars of different compositions. The typical constituents produced by the low temperature process (350° to 500° C.) are naphthenes and highly viscous oils. Under these conditions benzene is either absent or present in traces only, its place being taken by benzine (petroleum ether, etc.). Since large yields of tar may be obtained by this process on the technical scale, it should eventually be possible to prepare petroleum hydrocarbons in quantity from coal. As yet it is only remunerative where the cheap and readily accessible brown coal is used.

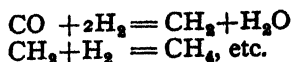
Direct Synthesis of Petroleum Hydrocarbons

Fischer-Tropsch Process.—It has long been known from the experiments of Sabatier and Senderens on the catalytic reduction of carbon monoxide under ordinary pressure that the final product is methane. Higher homologues are also obtained. In 1923 Franz Fischer



and Hans Tropsch of the Kaiser Wilhelm Institute for Coal Research in Mülheim showed that carbon monoxide and hydrogen in presence of

iron, cobalt, or nickel catalysts at 180-250° C. and atmospheric pressure form a mixture of aliphatic straight-chain hydrocarbons ranging from methane to waxes of high molecular weight. The mechanism of the reaction is probably complicated, but may be pictured as the formation and reaction of methylene radicals.



In 1936 commercial production in Germany was begun and during the war an annual output of over half a million tons of synthetic oil was obtained. The best catalyst was found to be a mixture of cobalt (100 parts), thorium oxide (5), magnesia (8), kieselguhr (200), and latterly medium pressures (about 10 atmospheres) were used.

A great range of saturated and unsaturated hydrocarbons are thus obtained and their value may be realised from the following table which gives some of the products obtained by the Germans from the several fractions.

Fischer-Tropsch Products

Fraction.	Primary Product.	Secondary Products.
"Gasol"	C ₃ H ₈ , etc.	Bottled gas, Propyl and butyl alcohols, etc.
b.p. 30-165° C.	Spirit	Motor spirit, O.N. 45-50
b.p. 165-230° C.	Middle oil	Diesel oil, C.N. 80
b.p. 230-320° C.	Heavy oil	Detergents, lubricating oils, etc.
b.p. 320-460° C.	Soft wax	Lubricating oils, fatty acid, etc.
b.p. 460° C.	Hard wax	Emulsifiable wax

O.N. = Octane number.

C.N. = Cetane number.

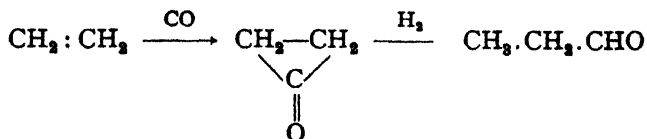
The Fischer-Tropsch process is now successfully worked in the United States, the carbon monoxide—hydrogen mixture (*synthesis gas*) being obtained by the oxidation of natural gas (methane) by oxygen.



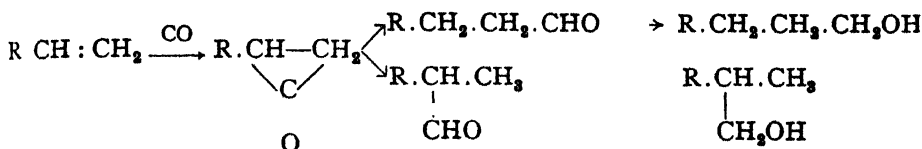
Greater efficiency has been obtained by use of the fluidisation technique in which the reactant gases are introduced into the bottom of the reaction chamber. The finely divided catalyst is carried along in the vapour stream and the reaction takes place in the turbulent mixture of gas and catalyst powder. This results in greater accessible catalytic surface and better temperature control.

Iso-synthesis.—It has already been stated that straight-chain paraffins and olefins are the main products of the Fischer-Tropsch process. In 1943 Fischer found that *iso*-paraffins are obtained when water-gas is passed over oxide catalysts such as thoria, thoria-alumina, etc., at 450° and 300 atmospheres pressure. *Iso*-butane is thus obtained in good yield. At lower temperatures alcohols, mainly *iso*-butyl, predominate, and at higher temperatures aromatic hydrocarbons are obtained along with a large quantity of methane.

Roelen or OXO Synthesis.—Dr Otto Roelen found that valuable secondary products result when olefins react with carbon monoxide and hydrogen in presence of Fischer-Tropsch catalysts in the liquid phase at 110-150° and 100-200 atmospheres pressure. The main products are aldehydes and alcohols. The process may be pictured as an addition of carbon monoxide at the double bond followed by hydrogenation. For example, ethylene gives propyl aldehyde in 80 per cent. yield.



Frequently mixtures will be obtained as shown by the following equation.



By this method long chain primary alcohols required for the manufacture of sulphate ester detergents are manufactured.

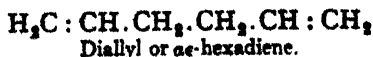
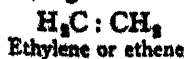
Synthol Process.—Reference may also be made to the use of catalysts under high pressures, by which carbon monoxide may be converted into methanol (see p. 153) and its higher homologues (*Synthol.*).

Bergius Process.—In another process invented by Bergius, coal, or the higher boiling fraction of coal tar is heated with hydrogen at pressures of 275 atmospheres or upwards in the presence of catalysts of the tin or molybdenum series. This method gives about 5 per cent. of lubricating oil, and up to 50 per cent. of benzine and Diesel motor oils, and appears to be of considerable industrial value. The plant required, however, is expensive and the catalyst difficult to recover. A British process involves a combination of coal and coal oil distillation together with "cracking," and yields a good quality of petroleum containing a large percentage of motor spirit.

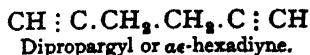
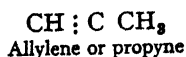
II.—UNSATURATED HYDROCARBONS

Nomenclature of the Open-chain Unsaturated Hydrocarbons

Those hydrocarbons containing one double bond are named after the corresponding saturated compounds by changing the termination -ane into -ylene, or according to the Geneva proposals into -ene. Should two or more pairs of doubly linked carbon atoms be present, this is indicated by the ending -diene, -triene, etc. The position of the double bond is shown by prefixing the letter or number of the first atom of the doubly bound pair, *e.g.* :—



Similarly, the names of hydrocarbons containing one or more triple bonds end in -yne, -diyne, -triyne, etc.

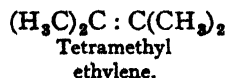
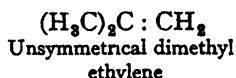
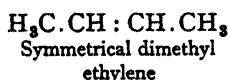


These compounds may also be described as alkyl derivatives of acetylene, *e.g.* allylene or methylacetylene.

1. Olefins, or Hydrocarbons of the Ethylene Series

Those aliphatic hydrocarbons which differ by a deficiency of two hydrogen atoms from the corresponding paraffins possess the general formula C_nH_{2n} , and take their name from ethylene, the first member of the series. It should be noted that no compound corresponding to methylene, CH_2 , is known to exist. All the hydrocarbons of this group contain two of their carbon atoms linked together with a double bond (*e.g.* $\text{H}_2\text{C} = \text{CH}_2$) which is consequently termed the ethylene bond. Isomeric with the olefins are the cycloparaffins, also of the general formula C_nH_{2n} , but possessing a closed ring structure in place of the open chains of the ethylene series.

The nomenclature of the olefins is discussed above, but simpler compounds are frequently designated as substituted ethylenes:—



The structural formula for ethylene might be written either as I or II, both of which represent the carbon atoms as tetravalent. Of these

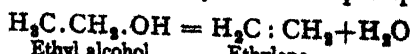


alternatives the former is adopted for the following reasons. If structure II containing two free valency bonds were correct, we should expect that ethyl, CH_3-CH_2- , with one free bond would resemble ethylene in being a stable compound. This, however, is not the case. The ethyl radical can be prepared, but it is exceedingly reactive and has only an ephemeral existence under ordinary conditions (see p. 103). Molecular models of type I possess a certain rigidity of structure, which is in agreement with the properties of ethylene derivatives, as illustrated by the existence of stable *cis* and *trans* isomerides such as fumaric and maleic acids. On the other hand, each half of the molecule according to formula II rotates freely about the central single bond, as in the case of ethane derivatives. This structure should not give rise to *cis* and *trans* isomerism.

Formation of the Olefins

The following methods are of general application.

1. The dehydration of alcohols by means of phosphoric acid.



Pure alumina has also been found to act as an energetic catalyst in splitting off the elements of water from alcohols, and olefins may be prepared by passing the vapour of an alcohol over alumina heated to 300°.

Secondary and tertiary alcohols lose water more readily than the primary compounds.

Many tertiary alcohols pass into unsaturated hydrocarbons with extraordinary ease, sometimes spontaneously at the moment of their formation, or merely on distillation. For this reason olefins are frequently produced by the action of ketones on alkyl magnesium halides (see Grignard reaction), particularly when an excess of the latter is employed.

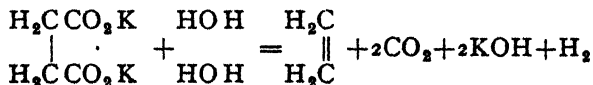
2. The action of ethyl alcoholic sodium or potassium hydroxide on the alkyl halides, particularly the iodides.



Ethers are also obtained, the ratio of olefin to ether depending on the conditions of the experiment, and the constitution of the halide. The greatest tendency for olefin formation is shown by compounds with halogen bound to a tertiary carbon atom, and the least when it is bound to a primary carbon atom. This is shown by the following examples.

Ethyl bromide	→	1 per cent. ethylene
<i>n</i> -Propyl bromide	→	20 per cent. propylene + 60 per cent. propyl ethyl ether
<i>iso</i> -Propyl bromide	→	75 per cent. propylene
<i>tert.</i> -Butyl iodide	→	Only butylene

3. The electrolysis of concentrated aqueous solutions of the potassium salts of certain saturated dicarboxylic acids; e.g. ethylene from potassium succinate.

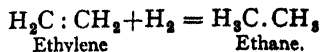


Properties.—In their physical properties the olefins closely resemble the paraffins. The lower members from C_2H_4 to C_4H_8 are gases, the intermediate ones are liquids and the highest are solids. They burn with a smoky and very luminous flame. The boiling-points of corresponding hydrocarbons of the two series lie very close together, but the melting-points of the olefins are a little lower than those of the paraffins. Most of the olefins are readily soluble in alcohol and practically insoluble in water. For the lower members the specific gravity at the melting-point is 0.63, and rises with increasing molecular weight to the neighbourhood of 0.79.

In their chemical behaviour, which differs very considerably from that of the paraffins, the most characteristic property is that of addition. The double bond in these hydrocarbons is capable of taking up two monovalent atoms or groups, becoming converted into a single bond, with the formation of paraffins or their substitution products. These

additive properties are found also in other classes of compounds and may therefore be treated a little more fully at this stage.

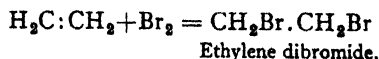
By union with hydrogen the olefins are transformed into paraffins of the same number of carbon atoms :—



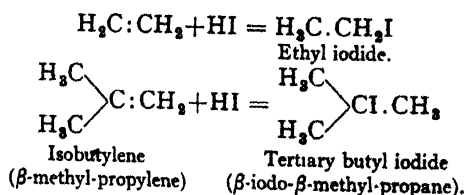
The addition of hydrogen to ethylene hydrocarbons used to be carried out by heating with hydriodic acid and phosphorus, but is now effected more rapidly and conveniently by **catalytic hydrogenation**. Sabatier, Senderens and Mailhe found that hydrogen adds on directly to unsaturated compounds at a high temperature in the presence of finely divided nickel, and the same change may be induced even more readily, without the addition of external heat, by the catalytic action of finely divided platinum or palladium.

In general, catalytic hydrogenation finds frequent application in laboratory and factory for the reduction of unsaturated organic compounds with gaseous hydrogen (see hardening of fats, p. 214). It is frequently employed to detect and determine the number of double bonds in unsaturated compounds.

Olefins readily unite with **halogens** and iodine chloride to form dihalogen derivatives. Of the three halogens, chlorine is the most reactive and iodine the least.



The addition of **hydrogen halides**, of which hydriodic acid is the most reactive, leads to the production of alkyl halides. In this reaction, if it is possible for the addition to take place in more than one way, the halogen usually attaches itself to that carbon atom which is united to the smaller number of hydrogen atoms (*Markownikoff rule*).

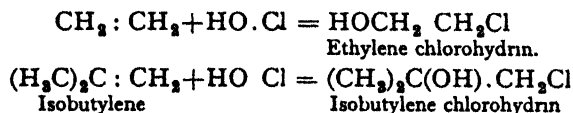


Although the Markownikoff rule holds generally for combination with hydriodic acid, many conflicting results have been reported for the addition of hydrogen bromide to olefins and especially to unsaturated halides of the type of allyl bromide, $\text{CH}_2:\text{CH}.\text{CH}_2\text{Br}$, and vinyl bromide, $\text{CH}_2:\text{CHBr}$. Investigations by Kharasch¹ have shown that the *pure* compounds react normally with hydrogen bromide according to the above rule, but that the direction of the addition is reversed either

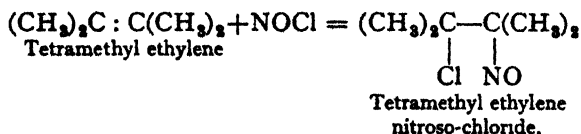
¹ M. S. Kharasch and F. R. Mayo, *J.A.C.S.*, 1933, 55, 2468; Kharasch and M. C. McNab: *ibid.*, p. 2531; Kharasch, *ibid.*, 1934, 56, 712.

in the presence of a peroxide such as benzoyl peroxide or in some cases merely on bubbling air or oxygen into the olefinic compound before use, which is sufficient to generate traces of peroxide. This reversal is known as the *peroxide effect*. Since allyl bromide usually contains traces of peroxide formed in contact with air, it behaves abnormally unless it is purified before use or the reaction is carried out in the presence of an antioxidant (*e.g.* diphenylamine or hydroquinone) which destroys the peroxide. With the still more sensitive vinyl bromide and vinyl chloride an antioxidant is essential for the normal reaction to take place. Olefinic hydrocarbons appear to be less sensitive and with them addition generally occurs normally unless a peroxide is added. Owing to its strong reducing action hydrogen iodide always yields the normal product, even in the presence of peroxides.

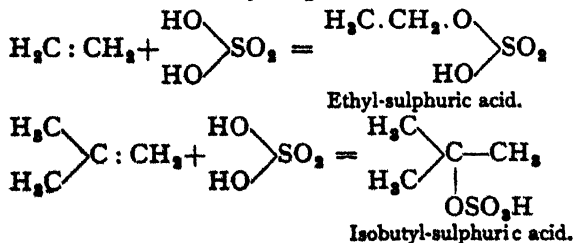
Aqueous hypochlorous acid converts the olefins into chlorohydrins (see also p. 261), in which case the hydroxyl group links itself preferably to the less hydrogenated carbon atom. Similar results are obtained with dilute chlorine water or bromine water¹ (Read). The interaction of ethylene with chlorine and water is the basis of the production of more than fifty commercial organic chemicals, which include ethylene glycol, ethylene oxide, dichlorethyl ether, etc.



The olefins also combine directly with nitrogen trioxide, nitrogen dioxide, nitrosyl chloride and nitrosyl bromide to form respectively nitrosites, nitrosates, nitroso-chlorides and nitroso-bromides. These additional compounds have proved of great value in terpene investigations.

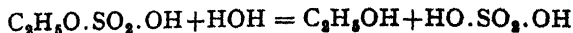


With concentrated sulphuric acid the olefins yield alkyl-sulphuric acids, also known as alkyl hydrogen sulphates, the acidic radical (*cf.* addition of hydrogen halide) attaching itself to that carbon atom united to the smaller number of hydrogen atoms²:

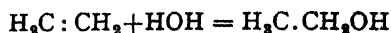


¹ J. Read and co-workers, *J.*, 1920, 1214; 1922, 989; 1928, 745. ² This reaction serves also for the separation of olefins from paraffins, the latter being scarcely affected.

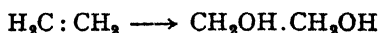
On boiling the alkyl-sulphuric acids in aqueous solution they decompose to form an alcohol and sulphuric acid :



In this manner it is possible to effect the indirect addition of the elements of water to the olefins, converting them into alcohols. Great quantities of ethyl and isopropyl alcohols, etc. are now manufactured by this method from olefins such as ethylene, propylene, etc.

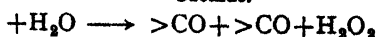
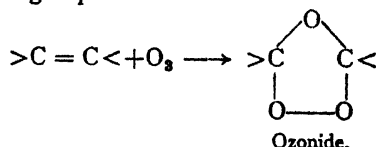


The olefins are very easily oxidised. Dilute alkaline permanganate solutions are rapidly decolorised by them, and the olefin converted into a dihydric alcohol.



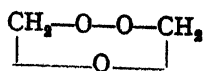
On more vigorous oxidation (chromic acid, ozone) the chain is ruptured at the double bond, with the formation of aldehydes, ketones and acids.

It was shown by Harries in a series of investigations that, if olefins and other unsaturated substances either in the pure state or in aqueous solution are treated with ozone,¹ they form compounds containing a molecule of ozone attached to each double bond. On warming these explosive ozonides with water, they are decomposed into aldehydes or ketones, and hydrogen peroxide.



This reaction offers a valuable method of determining the position of the double bond in an olefinic compound (see oleic acid).

The formulation of the ozonides given above is due to Staudinger who pointed out that in ozonide formation the carbon-carbon bond must be broken, since decomposition with water does not yield even a trace of the original compound and reduction gives no glycol. Rieche² has substantiated the Staudinger formula by a series of careful investigations. He showed that the properties of simple ozonides and the corresponding peroxides are very similar. For instance, ethylene ozonide and dimethyl peroxide are both low-boiling, mobile liquids of piercing smell, very



Ethylene ozonide



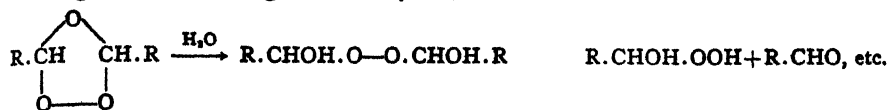
Dimethyl peroxide

sensitive and explosive, and exploding when treated with strong alkali or sulphuric acid. He showed further that the primary products of ozonide decomposition in presence of water are hydroxy-peroxides

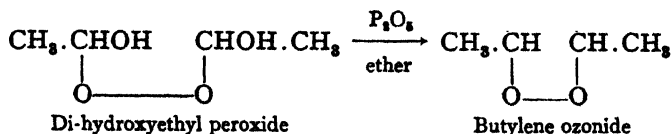
¹ For a survey of ozonisation see L. Long, *Chem. Reviews*, 1940, **27**, 437.
R. Meisler and H. Sauthoff, *Annalen*, 1942, **553**, 187.

² A. Rieche,

resulting from fission of the ether linkage, and these hydroxy-peroxides undergo further change to aldehydes, etc.



Finally Rieche found it was possible to reverse the above process and by removing water from di-hydroxyethyl peroxide with phosphorus pentoxide in ether succeeded in synthesising butylene ozonide.



Detection of the Ethylene Double Bond

(a) *Baeyer's Permanganate Test*.—According to Baeyer, alkaline permanganate is a general reagent for the recognition of unsaturated compounds. The test is carried out in aqueous solution by addition of a little sodium carbonate or bicarbonate and a drop of potassium permanganate. The colour of the latter rapidly disappears and a brown flocculent precipitate of a hydrated oxide of manganese forms. With compounds such as aldehydes, which already possess reducing properties, the reaction obviously gives no information as to the presence or absence of ethylene double bonds.

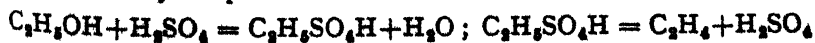
(b) *Addition of Bromine*.—Unsaturated compounds frequently absorb bromine with great ease, as is shown by shaking them with bromine water, when the colour disappears. It should be emphasised, however, that a number of substances are known, which, despite the presence of double bonds in the molecule, do not take up bromine.

(c) *Prileschajew Reaction*.—Double bonds are now detected and their number in a molecule estimated by oxidation with sodium perbenzoate. Ethylene oxides are formed.



The reagent can also be used for determining the position of double bonds in ring compounds as, for example, in cadinene, p. 416.

Ethylene, $\text{H}_2\text{C}=\text{CH}_2$, occurs to the extent of 4 to 5 per cent. in coal gas, and is usually prepared in the laboratory by heating one part of alcohol with four parts of concentrated sulphuric acid. In this reaction ethyl-sulphuric acid is first formed, and on further heating



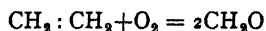
breaks up into ethylene and sulphuric acid. The gas is purified by bubbling through sodium hydroxide and concentrated sulphuric acid,

in order to remove traces of carbon dioxide, sulphur dioxide, alcohol and ether. A less impure ethylene may be prepared by adding alcohol, drop by drop, to syrupy phosphoric acid heated to 220° .

There are several methods for the preparation of ethylene on the industrial scale. In this country the dehydration of ethyl alcohol is used (p. 151), but in America it is obtained in enormous quantities by the cracking of petroleum, ethylene being one of the important constituents of cracked gas. It is also manufactured by pyrolysis of a mixture of ethane and propane.

In 1941 in the U.S.A. 60,000 tons of ethylene from petroleum were used in the manufacture of plastics. Many chemicals such as ethylene glycol, ethylene dichloride, ethylene chlorhydrin, styrene, etc., are now being manufactured from ethylene.

Properties.—Ethylene is a colourless gas possessing a faint ethereal smell; it is only slightly soluble in water, but more so in alcohol and ether. It burns with a luminous flame and forms an explosive mixture with oxygen. When led into bromine, rapid combination ensues with the formation of ethylene bromide, $C_2H_4Br_2$. Other properties of ethylene have been already described above. The oxidation of the gas by means of atmospheric oxygen was examined by Willstätter and Bommer, who found that formaldehyde was obtained in good yield. In view of the



almost unlimited uses of formaldehyde, this reaction may yet prove of industrial importance.

Ethylene is now being utilised in an interesting manner in the fruit industry. When intended for transportation to considerable distances fruit is gathered and packed before it is fully ripe. On arrival at its final destination it is maintained for a few days in an atmosphere containing a small proportion of ethylene, which rapidly develops the colour and completes the ripening.

Other important olefins are propylene, $CH_3 \cdot CH : CH_2$, and isobutylene, $(CH_3)_2C : CH_2$, both of which are obtained from petroleum. In the U.S.A. approximately 150,000 tons of isopropyl alcohol and acetone are prepared from propylene every year.

Among the pentenes or amylenes, a mixture of which is obtained industrially by heating fusel oil with zinc chloride, trimethyl-ethylene or β -isoamylenes is of special interest. It is employed under the name of *pental* as a narcotic of short duration, and also serves for the preparation of tertiary amyl alcohol.

2. Diolefins

For the *nomenclature* of these compounds compare p. 119.

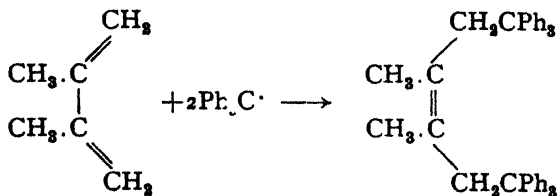
In *properties and chemical behaviour* the diolefins show many resemblances to the olefins. They differ from the acetylenes in forming no copper or silver compounds. On the other hand, they give precipitates

with a solution of mercuric chloride. They frequently contain conjugated double bonds.

Detection of Conjugated Double Bonds.—It is important to determine whether or not the double bonds in a diolefin are conjugated. Three useful methods may be cited.

1. *Diels-Alder Reaction.*—Many compounds which like butadiene possess conjugated double bonds combine quantitatively with acrylic aldehyde, maleic anhydride, and other compounds containing the $\cdot\text{CH}:\text{CH}\cdot\text{CO}\cdot$ group. This is known as the *Diels-Alder* reaction (see p. 450) and furnishes another example of 1:4 addition already discussed on pp. 14 and 15.

2. *Reaction with Triphenylmethyl Radical.*—Conant and Chow¹ showed that the triphenylmethyl radical (see p. 561) reacts at the 1 and 4 positions with conjugated diolefins. Thus 2:3-dimethylbutadiene reacts in the following manner:—



3. *Ultra-violet Absorption Spectra.*—An isolated double bond is known to have a maximum absorption at 185 $m\mu$ or less. A second double bond introduced into the molecule and separated from the first double bond by one or more methylene groups does not alter the position of the maximum absorption though it approximately doubles the intensity of absorption. If, however, the two double bonds are conjugated (a shift of between 15 and 45 $m\mu$ towards the visible results (see p. 88)).

Formation.—Diolefins are obtained from the dibromo-substitution products of the saturated hydrocarbons by removing hydrogen bromide with alcoholic potash or quinoline; by heating the phosphates of diamines, and by the *exhaustive methylation* of certain cyclic bases. Since these compounds have recently been employed in the technical preparation of artificial caoutchouc, various synthetic methods have been devised for their manufacture, which are given in more detail under caoutchouc.

Allene, $\text{H}_2\text{C}:\text{C}:\text{CH}_2$, may be prepared by the electrolysis of potassium itaconate; also from tribromo-propane, $\text{CH}_2\text{Br}\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$, by removal of hydrogen bromide and bromine. A naturally occurring allene derivative is *mycomycin*, which contains in addition two triple bonds and several double bonds.

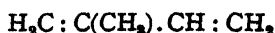


Mycomycin

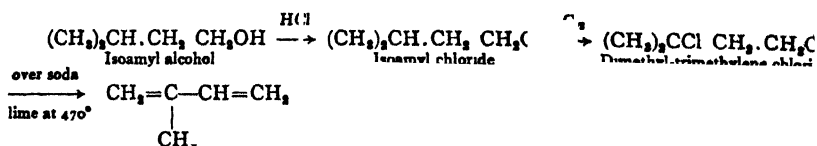
¹ J. B. Conant and B. F. Chow, *J.A.C.S.*, 1931, 53, 1941.

Butadiene, $\text{H}_2\text{C}:\text{CH}:\text{CH}:\text{CH}_2$, is obtained by the exhaustive methylation of N-methyl-pyrrolidine. The manufacture of butadiene is dealt with on p. 423, and its chemical behaviour on p. 15.

Isoprene, β -methyl-butadiene (β -methyl-divinyl),



is the most important hydrocarbon of this series. As it is produced together with trimethylethylene and dipentene by the dry distillation of caoutchouc, it is of importance in connection with the constitution of the latter. Isoprene may be prepared technically by various methods, e.g. from the isoamyl alcohol of fusel oil (p. 155) in the following stages



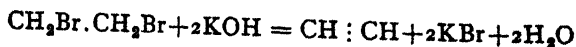
Isoprene is a liquid, b.p. 37° ; when heated to 300° under pressure it yields dipentene. In contact with sodium it polymerises to a rubber.

Isoprene is also of interest in connection with the chemistry of the carotenoids and the terpenes (p. 391).

3. The Acetylene Hydrocarbons

Nomenclature.—In addition to the details given on p. 120, it may be mentioned that compounds of this series are frequently named as substitution products of the first member, acetylene, $\text{CH}:\text{CH}$; e.g. 3-butyne or ethyl-acetylene, $\text{C}_2\text{H}_5.\text{C}:\text{CH}$.

Formation.—1. They can generally be prepared from the monohalogen substitution products, or the dihalogen addition products, of the ethylene hydrocarbons, by heating with alcoholic potash, e.g.:



An alcoholic solution of sodium or potassium ethoxide gives better yields, as there is then no tendency for the decomposition to stop at the intermediate stage of vinyl bromide.

2. Aldehydes and ketones also serve for the preparation of the acetylenes. With phosphorus pentachloride they are converted into dichloro-paraffins, which with potassium hydroxide yield acetylenes:



3. Acetylene and its homologues are also formed by the dry distillation of organic compounds and are therefore present in coal gas.

Properties and Chemical Behaviour.—In physical respects the acetylenes resemble the paraffins and olefins. The lower members of the series up to crotonylene, C_4H_6 , are gases, then follow liquids and finally from $C_{16}H_{30}$ upwards they are solids.

The chemical behaviour of the acetylenes shows them to be strongly unsaturated. They unite readily with hydrogen, halogens and hydrogen halides, in two stages, each of which corresponds to the addition of one molecule of these substances. If two molecules of halogen acid are



taken up, both halogen atoms attach themselves to the same carbon atom. Under certain conditions *polymerisation* may take place, *e.g.* acetylene, C_2H_2 , polymerises to form benzene, C_6H_6 ; and dimethyl-acetylene, C_4H_6 , to hexamethyl-benzene, $C_{12}H_{18}$. This is an important method of passing from the aliphatic to the aromatic series, and the acetylene condensation is to be regarded as the main, though not the only, source of aromatic compounds in coal tar.

A characteristic of acetylene and its monoalkyl-substitution products, $R\text{C} : \text{CH}$, is the property of giving solid crystalline precipitates with ammoniacal solutions of silver and cuprous salts. In this reaction the hydrogen of the CH -group is substituted by metals to form acetylides of the type of copper acetylide, C_2Cu_2 , which are explosive and regenerate the original hydrocarbon on warming with hydrochloric acid. By means of these metallic compounds acetylene may be purified and separated from other hydrocarbons.

ACETYLENE, $\text{CH} \equiv \text{CH}$.

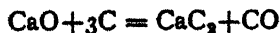
Acetylene was first observed by E. Davy in 1836 and later studied more intensively by Berthelot, who prepared it from its elements by causing an electric arc to pass between two carbon electrodes in an atmosphere of hydrogen.



Preparation.—Acetylene is readily prepared by the action of water on calcium carbide :



The carbide is obtained industrially by heating quicklime with 'coke' in an electric furnace, when the chief reaction takes place according to the equation



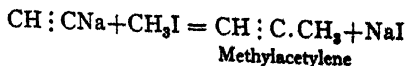
An important new source of acetylene is natural gas, which on pyrolysis gives acetylene. This method of manufacturing acetylene may be greatly developed in the future.

Properties.—Acetylene is a colourless poisonous gas of peculiar ethereal smell; it may be liquefied at 0° under a pressure of 26 atmospheres. At room temperature it dissolves in about its own volume of water, but it is considerably more soluble in organic liquids. Acetone for example, at 15° takes up under ordinary pressure twenty-five times its own volume of acetylene. Acetylene is an endothermic compound and, as might be expected, is explosive, especially in the liquid state. Under the influence of a blow or an electric spark and particularly when detonated by fulminate of mercury, acetylene decomposes spontaneously into its constituents with evolution of light and heat: $C_2H_2 = 2C + H_2$. Many disastrous explosions followed the first application of liquid acetylene to illumination on the large scale, as a result of which the manufacture and storage of the liquefied gas were forbidden by law. Subsequently it was discovered that when acetylene is dissolved in acetone, or admixed with other gases, especially ethylene or oil gas, it is insensitive to detonation, even under high pressures, and may then be used with safety.

Under the influence of heat it undergoes polymerisation, three molecules combining to give one molecule of benzene, much tar being formed also. Since acetylene may be prepared from its elements this reaction furnishes a complete synthesis of benzene. Another polymerisation of importance and one of more recent date (1940) is Reppe's discovery that four molecules of acetylene and a nickel catalyst give cyclo-octatetraene (p. 391), a substance of great theoretical interest.

As mentioned above, both hydrogen atoms of acetylene are replaceable by metals, and the formation of the red copper compound, C_2Cu_2 , may be utilised for the detection of very small amounts of the gas. In the dry state the acetylides of copper and silver are extraordinarily explosive. Under the catalytic influence of mercuric salts, acetylene combines with water to form acetaldehyde, which may readily be oxidised to give acetic acid. During recent years this process has been developed on the large scale, and adapted with great success to the manufacture of acetic acid. It is also used in the manufacture of acetic anhydride (p. 208).

Sodium acetylide $CH : CNa$, is formed by the action of acetylene on a solution of sodium in liquid ammonia. Disodium acetylide can similarly be formed. These acetylides are used to prepare acetylene homologues by interaction with alkyl halides in liquid ammonia.



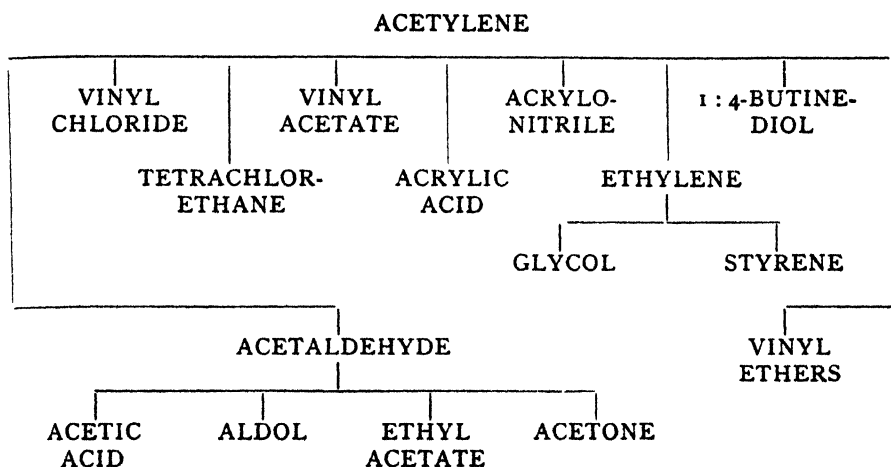
Technical Applications of Acetylene¹

The technical possibilities of acetylene have long been recognised and have been used for the manufacture of acetaldehyde, acetic acid, etc., but its commercial exploitation has been seriously retarded by its instability

¹ "Acetylene in Chemical Industry" by N. Booth, *Chem. and Ind.*, 1952, 812.

under high pressure. Thanks largely to the work of Dr Walter Reppe of the I.G. Farben and a huge team of collaborators, means have been devised for handling acetylene safely at high pressures (200 atmospheres), chiefly by the use of a diluent such as nitrogen. The work illustrates the necessity of fundamental research in industrial ventures, for Reppe's success was largely due to his elucidation of the mechanisms of acetylenic reactions and in particular the rôle played by the catalysts.

Some idea of the modern technical applications of acetylene may be obtained from the following diagram.¹

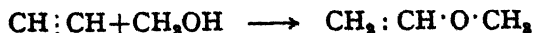


Recent developments may be divided into three main processes—*vinylation*, *ethinylation*, and *carbonylation*.

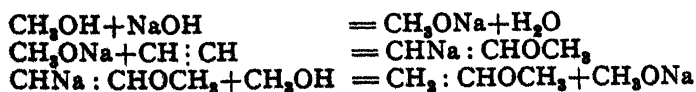
Vinylation.—This term denotes the interaction of acetylene and certain classes of compounds such as alcohols, phenols, carboxylic acids, and amines which contain “active” hydrogen atoms to give vinyl derivatives. Under the influence of alkaline catalysts and high pressure addition occurs at the triple bond with formation of an olefinic linkage.



Methyl vinyl ether, for example, is formed from methyl alcohol and acetylene.



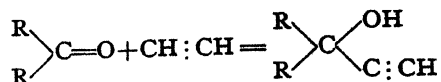
The mechanism is :



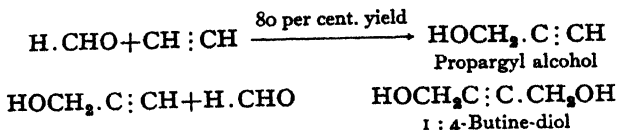
Ethinylation.—Ethinylation means the interaction of acetylene with organic substances, the acetylenic linkage remaining intact in the products.

¹ From *Manufacturing Chemist*, 1947, 28, 255.

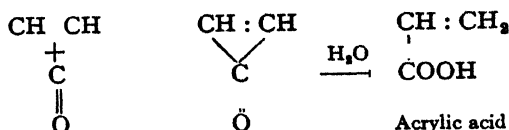
The success of this process depended on the daring use for the first time of metallic (copper, silver, etc.) acetylides. The most important applications are the formation of *alkinols* from acetylene and aldehydes or ketones.



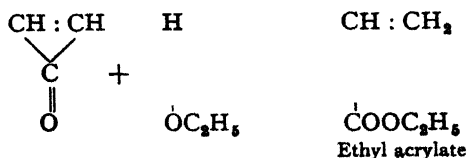
The method is illustrated by the preparation of *propargyl alcohol* and 1 : 4-*butine-diol* from acetylene and formaldehyde.



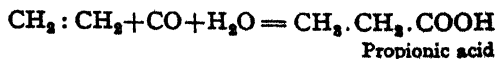
Carbonylation.—Carbonylation is effected by the reaction of acetylene and carbon monoxide in the presence of hitherto unused catalysts, the metallic carbonyls. With water carboxylic acids are obtained. The process may be pictured as occurring through the formation of an intermediate cyclopropenone.



With alcohols and amines in place of water esters and amides are formed, *e.g.*



A most interesting extension of this process is the preparation of carboxylic acids from olefins, carbon monoxide, and water with nickel carbonyl as catalyst, a temperature of 200-300° C. and pressure of 150-350 atmospheres being employed. Thus propionic acid is obtained from ethylene.



The process is obviously allied to the OXO process outlined on p. 119.

The above account gives only a slight idea of the potentialities of the Reppe processes, which will certainly find application not only in Germany but also in this country and the United States.

II

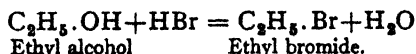
Halogen Derivatives of the Hydrocarbons

The halogen derivatives of the hydrocarbons provide the most valuable starting material for the synthesis of organic compounds, and if only for this reason merit description in some detail. In addition it may be noted that several of them, such as chloroform, CHCl_3 , and iodoform, CHI_3 , are extensively used in medicine.

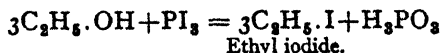
I.—HALOGEN DERIVATIVES OF THE PARAFFINS

Halogens normally function as monovalent elements, and a hydrocarbon such as methane would therefore be expected to yield four chlorine derivatives, CH_3Cl , CH_2Cl_2 , CHCl_3 and CCl_4 , as well as four bromine, iodine and fluorine compounds. Ethane, however, gives rise to nine instead of six chloro-derivatives, since in this case position isomerism is possible (*cf.* p. 11).

Methods of Formation.—1. The monohalogen derivatives or alkyl halides are most conveniently prepared from the corresponding alcohols, by replacing the hydroxyl group of the latter with halogen, either by the action of halogen acids,

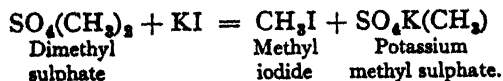


or of halogen compounds of phosphorus,



In the latter case, at all events in introducing bromine and iodine, it is not always necessary to employ previously prepared phosphorus halide, this being usually formed during the course of the reaction. For example, ethyl iodide may be obtained by adding powdered iodine to a mixture of alcohol and red phosphorus, and warming to complete the reaction.

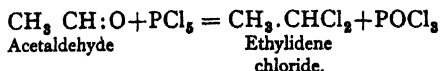
2. Alkyl halides are readily prepared by treating an aqueous solution of a metallic halide with dimethyl or diethyl sulphate. In this case only one of the alkyl groups takes part in the reaction, *e.g.*



3. Halogen derivatives are also obtained by the action of halogens on the paraffins (p. 106). Chlorine, for example, reacts with methane to yield CH_3Cl , CH_2Cl_2 , CHCl_3 and CCl_4 . The action of chlorine is particularly energetic in sunlight or in the presence of iodine, iron or antimony chloride (*chlorine carriers*); bromine reacts most easily when the reagents are warmed, or in the presence of aluminium bromide; iodine, however, has no action on the paraffins, unless in the presence of some substance such as mercuric oxide or iodic acid, which is able to remove the hydriodic acid formed.

4. As has been mentioned on pp. 122 and 129, the hydrocarbons of the olefin and acetylene series combine with halogens and hydrogen halides to form substitution products of the paraffins.

5. On treating aldehydes and ketones with phosphorus pentachloride the oxygen of the carbonyl group is replaced by halogen to yield dichloro-compounds,



6. von Braun showed that certain dihalogen derivatives are readily obtained by the cleavage of cyclic amines with phosphorus pentachloride or bromide. N-Benzoylpiperidine, for example, on warming with phosphorus pentabromide, is converted smoothly into 1 : 5-dibromopentane.

The preparation of iodides from the chlorides and bromides is most conveniently effected by treating the latter with sodium iodide in acetone solution.

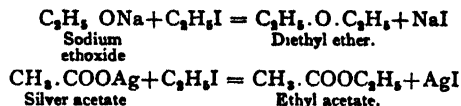
Properties.—A few of these derivatives, such as methyl chloride, are gaseous under ordinary conditions, but the majority are colourless, sweet-smelling liquids. Those of high molecular weight are solid. The iodo-compounds are only colourless when freshly prepared; they darken on standing, particularly under the influence of light, when decomposition occurs with the separation of free iodine. This may be minimised by the addition of some mercury, or a little finely divided ("molecular") silver. Among similarly constituted compounds, the chlorides possess the lowest boiling-point; the corresponding bromides boil approximately 25°, and the iodides 50°, higher than the chlorides. The iodides also possess the highest and the chlorides the lowest specific gravity, the figure sinking in each case as the hydrocarbon radical increases in magnitude. The halogen derivatives are not soluble in water, but dissolve readily in organic solvents such as alcohol, ether or carbon disulphide.

With regard to the *chemical properties* of the alkyl halides, it should be noted that, in spite of certain resemblances to the metallic halides, they differ characteristically from the latter in their behaviour towards silver nitrate. As is well known, the metallic halides such as potassium iodide are ionised in solution, and react instantaneously with aqueous or alcoholic silver nitrate, all the halogen being precipitated as insoluble silver halide. The halogen substitution products of the hydrocarbons, on the other hand, are practically non-electrolytes, and either do not react with silver nitrate or the reaction sets in gradually. Pure chloroform, for example, may be shaken with aqueous silver nitrate without any separation of silver chloride, while ethyl iodide only very slowly yields a precipitate of silver iodide.

It must not be concluded from this behaviour with silver nitrate that the halogen is particularly firmly bound in the substituted aliphatic hydrocarbons, since by means of suitable reagents it is readily eliminated and replaced by hydroxyl, alkoxyl, amino or other groups. On this ease of reaction depends the extraordinary utility of the halogen derivatives, and especially the alkyl iodides, for organic synthesis. The latter are

of great value in introducing alkyl groups into organic compounds, a process described in more detail in a later chapter.

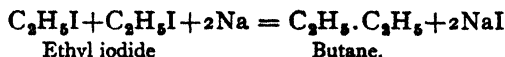
In order to replace hydrogen in the hydroxyl group of an alcohol or acid by an alkyl radical, the sodium derivative of the alcohol or the silver salt of the acid may be heated with alkyl iodide. In some cases thalious salts of the acids give even better results.¹



In a similar manner it is possible to replace a hydrogen atom attached to nitrogen or carbon, *e.g.*



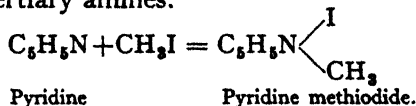
By means of the Würtz synthesis an iodine atom may be exchanged for an alkyl group,



The preparation of unsaturated hydrocarbons from alkyl halides has already been referred to on pp. 121 and 128.

It will also be seen later that the alkyl halides have been extensively applied to the preparation of organo-metallic compounds, particularly those of zinc and magnesium (p. 142).

A final indication of the many-sided reactivity of the alkyl halides is given by their power of forming addition compounds with other substances, such as tertiary amines.



Among the large number of substitution products of the paraffins known, the following are briefly described.

Methyl chloride, *chloro-methane*, CH_3Cl , is prepared by heating a mixture of methyl alcohol and hydrochloric acid with zinc chloride or sulphuric acid; also by heating trimethylamine hydrochloride, $\text{N}(\text{CH}_3)_3\text{HCl}$, obtained from the residual liquors in sugar manufacture, to 360° . It is a colourless, sweet-smelling gas which burns with a green-edged flame, and on being cooled condenses to a liquid, b.p. -23° . It comes on to the market in liquid form, and owing to the intense heat absorption resulting from its rapid evaporation, it is used for the production of low temperatures. **Ethyl chloride**, b.p. $+12^\circ$, is for the same reason employed as a local anaesthetic. It is manufactured by the addition of hydrochloric acid to ethylene in presence of a catalyst such as aluminium chloride.



¹ G. H. Christie and R. C. Menzies, *J.*, 1925, 127, 2369; C. M. Fear and R. C. Menzies, *J.*, 1926, 937.

Ethyl chloride is used extensively in the manufacture of lead tetra-ethyl ethyl-cellulose, and as a refrigerant.

Methyl iodide, CH_3I , may be prepared from methyl alcohol, iodine and red phosphorus. It is a liquid of pleasant ethereal odour, b.p. 44° and sp. gr. 2.27 at 25° . Under the influence of light it gradually darkens owing to the separation of iodine.

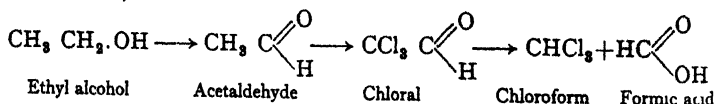
Ethyl iodide, $\text{C}_2\text{H}_5\text{I}$, is prepared from ethyl alcohol, iodine and red phosphorus. Boiling-point 72.5° and sp. gr. 1.975.

Ethylene dibromide, $\text{CH}_2\text{Br}-\text{CH}_2\text{Br}$, is obtained by passing ethylene gas into bromine. It is a colourless liquid of pleasant smell; b.p. 131° m.p. 8° . It is much employed as a solvent and for synthetic purposes.

Ethylene dichloride, $\text{CH}_2\text{Cl}.\text{CH}_2\text{Cl}$, is made from ethylene and chlorine. It is an excellent solvent and with sodium tetrasulphide forms the rubber substitute, Thiokol A.

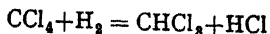
Chloroform, CHCl_3 , is a chlorination product of methane or methyl chloride, and is formed by the action of bleaching powder on various organic substances such as alcohol, acetone, acetic acid and its salts, and tartaric acid.

The *method of preparation*, also used on the technical scale, is to distil aqueous alcohol with bleaching powder. It is supposed that the first step in this reaction is the oxidation of alcohol to aldehyde, which next undergoes substitution to trichloraldehyde (chloral), this being then hydrolysed by the lime present in the bleaching powder to formic acid and chloroform,

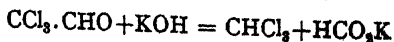


Acetone may be used instead of alcohol in this preparation.

Chloroform is manufactured in large quantities in the U.S.A. by the reduction of carbon tetrachloride with water and iron.



Chloroform prepared by any of the above methods is generally impure. It may be obtained in a very pure state, although at considerably greater expense, from chloral hydrate, which on heating with alkali decomposes into chloroform and the alkali salt of formic acid.



Properties.—Chloroform is a colourless mobile liquid, b.p. 62° and sp. gr. 1.491 at 17° . It has a sickly sweet smell and a burning taste, dissolves readily in alcohol and ether, but only sparingly in water.

Inhalation of its vapour brings about loss of consciousness, and for this reason it is largely used as an anaesthetic in surgical operations. Chloroform was discovered almost simultaneously by Liebig and Soubeiran in 1831, but its anaesthetic properties remained unknown till their discovery in Edinburgh by Simpson in the year 1848.

$$2\text{CHCl}_3 + 3\text{O} = 2\text{COCl}_2 + \text{Cl}_2 + \text{H}_2\text{O}$$
$$\text{CHCl}_3 + 4\text{KOH} = \text{HCO}_2\text{K} + 3\text{KCl} + 2\text{H}_2\text{O}$$

Potassium formate.

$$\text{C}_6\text{H}_5\text{NH}_2 + \text{CHCl}_3 + 3\text{KOH} = \text{C}_6\text{H}_5\text{NC} + 3\text{KCl} + 3\text{H}_2\text{O}$$

Aniline Phenyl isocyanide

Iodoform, CHI_3 , is produced by the action of iodine and caustic alkali on alcohol, acetaldehyde or acetone. This is known as the *haloform reaction*¹; in general it is given by any compound containing the group CH_3CO linked to carbon or hydrogen, or any group such as $\text{CH}_3\text{CH}(\text{OH})$ which may be converted into CH_3CO by the oxidising action of the reagent.

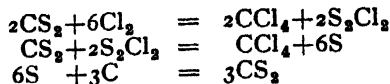
$$\text{C}_2\text{H}_5\text{OH} + 8\text{I} + 6\text{KOH} \rightarrow \text{CHI}_3 + \text{HCO}_2\text{K} + 5\text{KI} + 5\text{H}_2\text{O}$$

Potassium formate

Carbon tetrachloride, CCl_4 , is obtained by several methods on the industrial scale as a colourless liquid, b.p. 76° .

¹ For an excellent survey of the haloform reaction see R. C. Fuson and B. A. Bull, *Chem. Rev.*, 1934, 273.

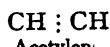
1. Action of chlorine on chloroform or carbon disulphide.

2. Chlorination of carbon disulphide with sulphur chloride (SCl_2).

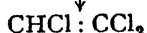
3. Chlorination of natural gas (methane).

It is largely used as a solvent for dry cleaning and degreasing and as a fire extinguisher.

A series of chlorinated compounds are valuable solvents and are used for "degreasing," etc. Many of them are toxic. They are all made directly or indirectly from acetylene.



Tetrachlorethane
(Main product)



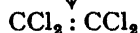
Trichlorethylen



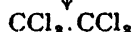
Dichloroacetylen



Pentachlorethane
(By-product)

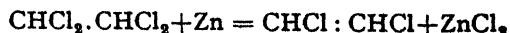


Tetrachlorethylen



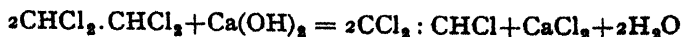
Tetrachlorethane, *acetylene tetrachloride*, b.p. 146.3° , $\text{CHCl}_2 \cdot \text{CHCl}_2$, is obtained with pentachlorethane as a by-product by the addition of chlorine to acetylene in presence of a catalyst, antimony tetrachloride, and some diluent, in the absence of which combination occurs explosively. It is a heavy non-inflammable liquid, which is used under the name of *Westron* as a solvent for cellulose acetate varnishes, for rubber and fats, and also as an insecticide.

Acetylene dichloride, *dichlorethylen*, $\text{CHCl} : \text{CHCl}$, is prepared industrially as a mixture of two isomerides (b.p. 48° and 60°) by treating *Westron* with zinc and water. It is sometimes used for



extractions in place of ether or light petroleum.

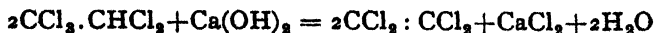
Trichlorethylen, *Westrosol*, $\text{CCl}_2 : \text{CHCl}$, is prepared from tetrachlorethane with lime.



It is used extensively as a degreasing agent and also as an anæsthetic (*trilene*); in the latter case care must be exercised as alkali readily converts it into the toxic dichloroacetylene.



Tetrachlorethylene, $\text{CCl}_2 : \text{CCl}_2$, is obtained commercially by heating **pentachlorethane** with lime.



It is used as a solvent in dry-cleaning. It gives on chlorination **carbon hexachloride**, *hexachloroethane*, C_2Cl_6 , which is used to make smoke-screens.

Chloropentanes. *n*- and *iso*-Pentanes occur in quantity in Virginia and other parts of the United States and may be chlorinated readily to give the isomeric chloropentanes from which by hydrolysis the amyl alcohols are prepared (p. 159).

II.—HALOGEN DERIVATIVES OF THE UNSATURATED HYDROCARBONS

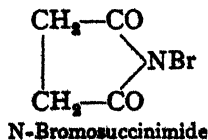
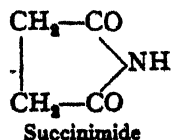
Many of these compounds are prepared by the partial removal from di-halogeno-compounds, etc., of hydrogen halides with alcoholic potash, calcium hydroxide, etc., trichlorethylene, tetrachlorethylene, and dichloroacetylene being, as we have seen, obtained in this way. Only in exceptional cases are the desired derivatives obtained directly by the action of halogens on unsaturated hydrocarbons, since the first action of the halogen is generally one of addition and not of substitution.

Halogen Substitution of Unsaturated Compounds

A notable example of substitution of an unsaturated compound is the "*hot chlorination*" of propylene at 500° , substitution occurring at the methyl group and not, as anticipated, addition at the double bond. **Allyl chloride** is prepared industrially by this method and serves as an intermediate in the manufacture of allyl alcohol and glycerol.

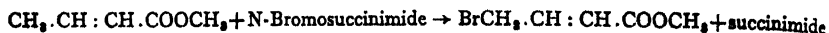


This substitution of the α -methylenic group (often referred to as the *allyl position*) is of little general value since many unsaturated compounds are decomposed at such high temperatures. It was therefore a great advance when Ziegler¹ found that bromination of the allyl position could be carried out at much lower temperatures with N-bromosuccinimide, a substance easily prepared by adding bromine to an ice-cold solution of succinimide in alkali.



¹ *Annalen*, 1942, 552, 80.

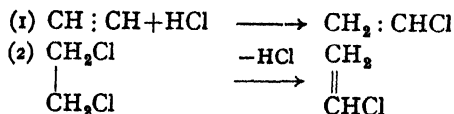
A good example of the application of the reagent is found in its reaction with methyl crotonate to give methyl 3-bromocrotonate a valuable synthetic reagent which can be used in the Reformatsky reaction.



The reactions are advantageously effected in carbon tetrachloride solution since the resulting succinimide is insoluble in this solvent and hence is easily removed.

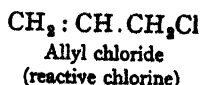
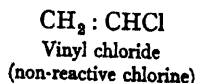
The most plausible explanation of the above substitutions at the allyl position is that they are brought about by chlorine or bromine atoms. They are thus radical reactions which differ considerably from ionic or molecular reactions. Indeed substitution at the allyl position is often used to detect free radicals (see p. 98).

Another unsaturated chloro-compound of importance is **vinyl chloride**¹ which is obtained either by the addition of hydrochloric acid to acetylene or the removal of this acid from ethylene dichloride by pyrolysis or caustic soda.



The *halogen derivatives of the olefins*, in which halogen is united to a doubly bound carbon atom, differ markedly from the corresponding paraffin derivatives in that the halogen is in general not replaceable by other radicals such as hydroxyl. Like the olefins themselves, they readily combine with halogens and halogen acids, and exist in geometrically isomeric forms.

Those halogen derivatives of the olefins in which, as in allyl chloride the halogen is attached to a singly bound carbon atom, resemble the paraffin compounds in the reactivity of the halogen.



One of the commonest unsaturated halogeno-compounds is allyl iodide, $\text{CH}_2:\text{CH}.\text{CH}_2\text{I}$, which is obtained from glycerol by heating with iodine and phosphorus. It is a colourless liquid, which smells of leeks and is frequently employed in syntheses for the introduction of the allyl group.

III.—ORGANIC FLUORINE COMPOUNDS¹

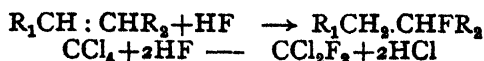
A separate section may appropriately be devoted to the organic fluorine compounds since their mode of preparation and properties differ considerably from those of their chlorine analogues, etc. Indeed un-

¹ The radical $\text{CH}_2:\text{CH}-$ is known as *vinyl*. ² F. Smith, *Ann. Reports*, 1947, 44, 86.

recently the fluorine compounds of carbon have been little more than chemical curiosities, but, thanks to intensive research, fluorination is now a commercial process both in the United States of America and Great Britain. This is to be welcomed since fluorine with its extreme electronegativity gives rise to substances of theoretical interest. Moreover, *fluorocarbons* are extraordinarily inert and are therefore valuable as non-inflammable, non-corrodible lubricants, plastics, etc. For example, polymerised *tetrafluoro-ethylene* is a chemically inert solid with excellent electrical properties. Fluoro-carbons are also used as refrigerants and are sold in this country under the trade name "Arcton" and in America as "Freon." An example is difluorodichloromethane CF_2Cl_2 (see p. 137).

Methods of Preparation.—(1) Elementary fluorine reacts with carbon at temperatures below 500° to give a solid monofluoride $(\text{CF})_n$ and at higher temperatures *carbon tetrafluoride* and a series of higher *fluorocarbons*. These can also be obtained by the controlled fluorination of hydrocarbons.

(2) Hydrogen fluoride forms fluoro-compounds either by addition to ethylenic linkages or by replacement of chlorine.



(3) A number of fluorine derivatives such as cobalt trifluoride are used extensively for preparative purposes. Cobalt trifluoride has one extremely reactive fluorine atom and is conveniently generated by adding cobaltous chloride, CoF_2 , to the compound to be fluorinated and passing fluorine into the mixture. The cobaltic fluoride, CoF_3 , thus generated *in situ* fluorinates by losing a fluorine atom and forming cobaltous fluoride. The latter combines with more fluorine and the continuous process goes on to completion.

(4) Pyrolysis is sometimes advantageously used. Thus tetrafluoroethylene is obtained by the pyrolysis of monochlorodifluoromethane.



III

Organo-metallic Compounds

The organo-metallic compounds are usually prepared by the action of metals, such as zinc, magnesium or mercury, on the alkyl iodides, and owing to their reactivity are frequently employed in synthetic reactions. The zinc and magnesium compounds are the most important of this class, and it is only recently that the simpler derivatives of the alkali metals have been carefully studied.

Sodium alkyls, e.g. sodium methyl, NaCH_3 , are obtained by the action of sodium on the corresponding mercury alkyls. In the pure

state they form colourless amorphous solids which are completely insoluble in indifferent solvents, and when heated decompose without melting. They are extremely sensitive towards oxygen, moisture and carbon dioxide, are inflammable in air and very reactive.

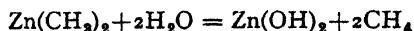
Zinc alkyls were discovered in 1849 by Frankland. They are obtained by the action of excess of zinc on alkyl iodides. The reaction is facilitated by using zinc in the form of the zinc-copper couple and by addition of ethyl acetate. Zinc alkyl iodides are first formed which decompose into zinc alkyls and zinc iodide on distillation.



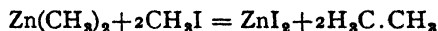
The zinc alkyls are colourless, unpleasant smelling liquids which boil without decomposition at relatively low temperatures in an atmosphere of carbon dioxide. They are spontaneously inflammable in air, and produce painful burns in contact with the skin. They were examined in detail by Frankland, who showed that they could be used for the synthesis of a variety of compounds, including alcohols and ketones.

Zinc methyl, $\text{Zn}(\text{CH}_3)_2$, b.p. 46° ; *zinc ethyl*, $\text{Zn}(\text{C}_2\text{H}_5)_2$, b.p. 118° ; *zinc propyl*, $\text{Zn}(\text{C}_3\text{H}_7)_2$, b.p. 146° .

With water they decompose to form paraffins and zinc hydroxide.

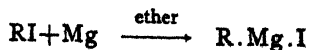


Paraffins are also produced on heating zinc alkyls to a high temperature with alkyl iodides.



Frankland's work on the metallic alkyls was extended to derivatives of other metals, e.g. trimethyl arsine, $\text{As}(\text{CH}_3)_3$ and trimethyl stibine, $\text{Sb}(\text{CH}_3)_3$, which first led to the belief that each element had a definite combining power and so laid the foundation of the modern theory of valency.

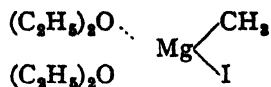
Organo-Magnesium Compounds.—Barbier in 1899 was the first to use magnesium in synthetic work, but it was left to his student Victor Grignard to realise in the following year the great possibilities of the method. For his researches in this field carried out over a period of years Grignard was awarded the Nobel Prize in 1912. One of the great advantages of Grignard's method is that the magnesium reagents do not require to be isolated, but can be used directly in ethereal solution, the ether functioning both as catalyst and solvent. Grignard showed that magnesium in the presence of dry ether interacts with numerous organic halogen substances to form compounds of the type RMgI which remain dissolved in the ether.



Reactions between metallic magnesium and alkyl or aryl halides in ethereal solution are known as *Grignard reactions* and compounds of the general formula $\text{R} \cdot \text{Mg} \cdot \text{Hal}$ as *organo-magnesium halides* or *Grignard reagents*.

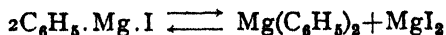
It was shown later by Tschelinzeff that the formation of these compounds also takes place slowly in other solvents such as benzene, toluene, and xylene, in the presence of a trace of ether. The amount of organo-magnesium halide formed is out of all proportion to the quantity of ether employed, from which it was concluded that in the Grignard reaction the ether plays the part of a catalyst.¹

If desired, the magnesium alkyl halides may be isolated in combination with two molecules of ether, *e.g.* CH_3MgI , $2(\text{C}_2\text{H}_5)_2\text{O}$. According to Meisenheimer these compounds are regarded as complexes of magnesium in which the metal occurs as the central atom with a co-ordination number 4.



As a result of their extraordinary reactivity and ease of preparation the organo-magnesium compounds have attained a position in synthetic chemistry unrivalled by that of any other class of compound.

An interesting development was the discovery by Schlenk² that an organo-magnesium halide exists in solution in equilibrium with magnesium halide and magnesium dialkyls or diaryls of the type MgR_2 .



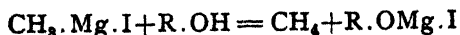
W. Schlenk, jun.³ confirmed the existence of this equilibrium by mixing magnesium diphenyl and magnesium iodide in ether and showing the presence after some time of phenyl magnesium iodide.



It has been found that both the magnesium compounds (RMgX and R_2Mg) react similarly though at different rates.

Grignard reagents undergo three main types of reaction as summarised below.

1. *Reaction with compounds containing reactive hydrogen.*—Substances such as water, alcohols, amines, etc., react readily with Grignard reagents, *e.g.*



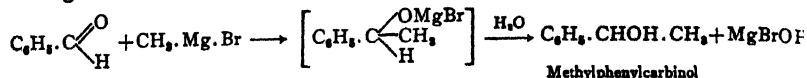
Tschugaeff showed that by measuring the methane so liberated the number of hydroxyl groups in a compound is determined, and Zerewitinoff applied the method to different types of compounds including primary and secondary amines.

The exclusion of water in the preparation of Grignard reagents is due to this reactivity.

2. *Addition to unsaturated linkages.*—The most important reaction of the Grignard reagents for synthetic purposes is their addition to the

¹ A chemical process, the velocity of which depends greatly upon the presence of some particular substance which is not itself used up in the chemical change, is termed a *catalytic reaction*, the substance in question being known as a *catalyst*. ² W. Schlenk and W. Schlenk, *Ann., Ber.*, 1929, 6a, 920. ³ *Ber.*, 1931, 64, 734.

double and triple bonds of aldehydes, ketones, nitriles, etc., followed by decomposition with dilute mineral acids. The process may be pictured as the Grignard reagent $R \cdot Mg \cdot X$ breaking up into two fragments, the radicals R and MgX , the former adding to the carbon atom of the multiple linkage and the MgX to the other atom, generally oxygen or nitrogen, *e.g.*



In a similar way a great number and variety of compounds can be synthesised, some of the more important being given in the following table

Formaldehyde	→	Primary alcohols
Other aldehydes	→	Secondary alcohols
Ketones	→	Tertiary alcohols
Esters	→	Tertiary alcohols
Acid chlorides	→	Ketones
Nitriles	→	Ketones

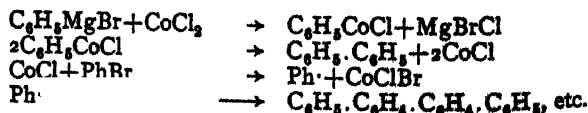
Many examples of the synthetic value of these reactions will be found throughout the book. The Reformatsky reaction, mentioned later, is similar in type to the Grignard.

The Grignard reaction sometimes takes a course different from that expected. Some aldehydes and ketones, for instance, react in the enolic form and are obtained unchanged at the end of the reaction. Ethyl acetoacetate and methylmagnesium iodide thus give methane and unchanged ethyl ester.¹ Other "abnormal" Grignard reactions include condensation and reduction.

3. *Formation of free radicals.*—Kharasch and his co-workers have shown that the reactivity of Grignard reagents is profoundly modified by the presence of metallic halides such as cobaltous chloride.² The results are best interpreted by the generation in solution of free radicals. As an illustration the formation of diphenyl in good yield from phenyl magnesium bromide and bromobenzene in presence of a small quantity of cobaltous chloride may be given.

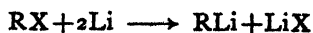


The diphenyl is derived from the Grignard reagent since replacement of the bromobenzene by *p*-bromotoluene or ethyl bromide also gives a good yield of diphenyl. The bromobenzene, however, is attacked by the free phenyl radical to give terphenyl, etc. This is characteristic of free radical reactions and together with the small amount of cobaltous chloride required provides strong evidence that a chain reaction involving free radicals occurs as follows :



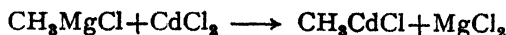
¹ A. Hepworth, *J.*, 1919, 125, 1205. ² For a general summary of this work see D. H. Hey, *Ann. Reports*, 1944, 42, 104.

Lithium Alkyls, etc.—Alkyl halides and lithium in dry ether yield *lithium alkyls* :

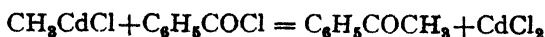


These compounds behave like Grignard reagents and are used in syntheses when the magnesium reagents are difficult to prepare.

Cadmium compounds are obtained by the addition of anhydrous cadmium chloride to Grignard reagents in ether :



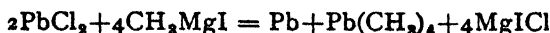
With acid chlorides they give ketones and are preferred to the Grignard



reagent since the reaction is easily arrested at the ketone stage.

In addition to the above compounds, alkyl derivatives of many other metals, including mercury, lead, and tin, have also been prepared. The mercury compounds HgR_2 are extremely poisonous liquids.

The **lead alkyls**, *e.g.* *lead tetramethyl*, $Pb(CH_3)_4$, b.p. 110° , possess a special interest as illustrating the tetravalency of lead. They are most conveniently obtained by acting on alkyl magnesium halides with lead chloride.



On being heated they decompose, liberating free alkyls which rapidly polymerise. **Lead tetraethyl** is prepared industrially from sodium-lead



alloy and ethyl chloride. It is added in small proportion to petrol as an "anti-knock" agent (*Ethyl petrol*).

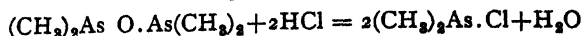
Organic Derivatives of Arsenic.—These were discovered as early as 1760, when Cadet observed the formation of a "fuming arsenical liquid" on heating potassium acetate with arsenic trioxide. But it was not until this reaction was investigated in detail by Bunsen that the structure of the cacodyl oxide thus produced was established. Bunsen proved that the cacodyl radical, $(CH_3)_2As$, occurred unchanged throughout a series of derivatives and so provided further support for the theory of radicals.

Cacodyl oxide, $[(CH_3)_2As]_2O$, b.p. 150° , is obtained by distilling a mixture of potassium acetate and arsenic trioxide. The liquid is insoluble



in water, possesses a nauseous odour (cacodyl=stinking) and its vapour is unbearably irritating to the mucous membrane. As prepared by the above method the oxide is contaminated with *tetramethyl-diarsine* (cacodyl), forming a mixture which fumes in air and may undergo spontaneous combustion. On distillation with hydrochloric acid the crude oxide is converted into *cacodyl chloride*, from which the pure oxide may

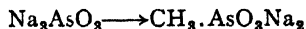
be regenerated by treatment with alkali. **Cacodyl chloride, dimethyl arsine chloride**, $(\text{CH}_3)_2\text{AsCl}$, boils at 100° and has an even more stupefying odour than the oxide. It is spontaneously inflammable in air. When



reduced with zinc or mercury in an atmosphere of CO_2 it yields **tetramethyl-diarsine, cacodyl**, $(\text{CH}_3)_2\text{As} \cdot \text{As}(\text{CH}_3)_3$. This is also a spontaneously inflammable liquid, which boils at 170° and possesses the same unpleasant physiological properties as the chloride and oxide. As Bunsen first showed, cacodyl behaves as an "organic element," uniting with oxygen, chlorine and sulphur, etc., to form the corresponding derivatives.

Cacodyl oxide may be oxidised slowly in air or more rapidly by use of mercuric oxide to give **cacodylic acid**, $(\text{CH}_3)_2\text{As} \begin{array}{c} \text{O} \\ \diagup \\ \text{OH} \end{array}$. The latter

is a weak acid, which melts at 200° and is odourless. Closely related to this compound is **methyl arsinic acid**, obtained as its disodium salt by direct methylation of sodium arsenite with dimethyl sulphate at 85° . Both of the above acids have been utilised medicinally in the form of their



sodium salts for the treatment of skin and other diseases. Various aromatic arsenic derivatives employed for the same purpose are described later.

Methyl dichloroarsine, CH_3AsCl_2 , has been used in warfare as a poison gas. Disodium methyl-arsenite, prepared as already indicated by the methylation of sodium arsenite, is treated with sulphurous acid to convert it into methyl-arsine oxide, which is then brought into reaction with gaseous hydrochloric acid to give methyl dichloroarsine. It may be separated from admixed methyl alcohol and hydrochloric acid by fractional distillation, and boils at 130° to 132° .

IV

The Alcohols

Classification.—The alcohols may be derived theoretically from the hydrocarbons by replacing a hydrogen atom of the latter by a hydroxyl group. Generally speaking, therefore, they may be regarded as alkyl hydroxides (in which the alkyl radical may be saturated or unsaturated) with a constitution resembling that of the metallic hydroxides. At the same time it should be emphasised that in their typical properties alcohols and inorganic bases show considerable differences. The inorganic bases are electrolytes and alkaline in reaction, the alcohols are non-electrolytes and neutral. As will be seen later, both alcohols and bases react with acids with elimination of water.

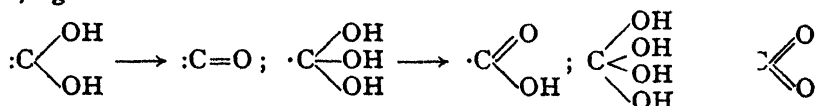
Corresponding to mono- and polyacid bases we have mono- and polyhydric alcohols. If one hydrogen in a hydrocarbon is replaced by OH we obtain a monohydric alcohol; if two hydrogens attached to *different* carbon atoms are exchanged for hydroxyls we obtain a dihydric alcohol, and so on. Alcohols are known containing three, four, five, six and more hydroxyl groups.

Examples : $\text{CH}_3 \cdot \text{OH}$
Monohydric alcohol
Methyl alcohol

$\begin{array}{c} \text{OH} \quad \text{OH} \\ | \quad | \\ \text{CH}_2 - \text{CH}_2 \end{array}$
Dihydric alcohol
Ethylene glycol

$\begin{array}{c} \text{OH} \quad \text{OH} \quad \text{OH} \\ | \quad | \quad | \\ \text{CH}_2 - \text{CH} - \text{CH}_2 \end{array}$
Trihydric alcohol
Glycerol.

If two or more hydroxyl groups are attached to the same carbon atom, they represent an unstable formation. In such cases, with few exceptions, water is eliminated and oxygen remains united to carbon by a double bond, *e.g.*



According as the hydroxyl group is linked to a primary, secondary or tertiary carbon atom (p. 103) we speak of a primary, secondary or tertiary alcohol.

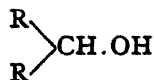
Primary alcohols therefore contain the group $-\text{CH}_2 \cdot \text{OH}$, in which the free bond is linked to carbon. On oxidation they are first converted into aldehydes, the group $-\text{CH}_2 \cdot \text{OH}$ being transformed into $-\text{CH} : \text{O}$. The latter on further oxidation form acids, containing the group $-\text{COOH}$ and having the same number of carbon atoms as the original alcohol.

Secondary alcohols contain the group $>\text{CH} \cdot \text{OH}$. These on oxidation are converted into ketones of the same number of carbon atoms, the group $>\text{CH} \cdot \text{OH}$ being oxidised to $>\text{C} : \text{O}$. On further oxidation the molecule breaks down, yielding acids containing a smaller number of carbon atoms.

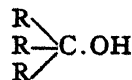
Tertiary alcohols contain the group $\begin{array}{c} \diagup \\ \text{C} \cdot \text{OH} \end{array}$. They break down on oxidation, giving ketones and acids, each containing fewer carbon atoms than the original alcohol.



Primary alcohol



Secondary alcohol

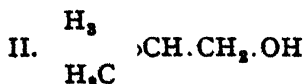


Tertiary alcohol.

Isomerism and Nomenclature.—As in the case of hydrocarbons, we may have structural isomerism among alcohols due to differences in the linking of the carbon chains (I and II), the primary alcohol which corresponds to the normally constituted hydrocarbon being termed a normal alcohol.

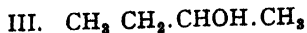


Normal primary butyl alcohol
or propylcarbinol

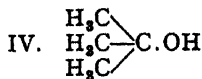


Isobutyl alcohol
or isopropylcarbinol.

Isomerism may also be occasioned by the different position of the hydroxyl in the molecule (I and III), or both these variations may occur together (I and IV).



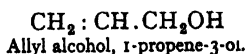
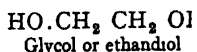
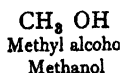
Normal secondary butyl alcohol
or methylethylcarbinol



Tertiary butyl alcohol or
trimethylcarbinol

A convenient nomenclature for such isomerides is obtained by considering them as substitution products of methyl alcohol, CH_3OH , by naming the latter carbinol and the higher alcohols as substituted carbinol (see above formulæ).

According to the Geneva nomenclature, the names of the alcohols are obtained from those of the hydrocarbons from which they are derived by replacing the final -e by -ol. Polyhydric alcohols are designated as diols, triols and so on.



If a hydroxyl group is attached to a side chain, the name of the latter takes the termination -ol.

MONOHYDRIC ALCOHOLS

As already mentioned, these may be derived from saturated or unsaturated hydrocarbons. The unsaturated alcohols differ from the saturated in their additive properties only, resembling them in all typical reactions, so that they are conveniently treated together.

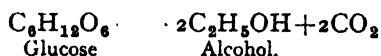
The *physical properties* of the monohydric alcohols vary from member to member, just as is the case with any other homologous series. The first members are mobile liquids—gaseous alcohols being unknown—after which follow those of oily consistency, and from dodecyl alcohol, $\text{C}_{12}\text{H}_{26}\text{OH}$, onwards they are wax-like solids. Solubility in water diminishes with increase in molecular weight, the first members of the series being miscible in all proportions, whereas the higher alcohols are quite insoluble. The lower compounds possess a characteristic alcoholic smell and taste, the intermediate members have an unpleasant smell, and those of high complexity are tasteless and odourless. For alcohols of similar structure the boiling-point rises regularly with increase of molecular weight. Each difference of CH_2 corresponds to a rise of approximately 20° . The highest members (above C_{16}) decompose on distillation, unless this is conducted under diminished pressure. Primary alcohols boil higher than the isomeric secondary, and these again higher than the corresponding tertiary compounds. The specific gravity is in all cases less than unity.

Methods of Formation.—(a) Alcohols may be obtained from alkyl halides by exchanging the halogen atom for hydroxyl, either by treating them with moist freshly prepared silver oxide at the ordinary temperature or with gentle warming, or by heating them with lead oxide and water.



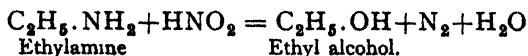
Alkalis bring about the same change, but tend to remove hydrogen halide, with the simultaneous formation of olefins. Tertiary halides readily undergo conversion into alcohol in contact with water alone.

(b) A method of great industrial importance is the formation of alcohols by the fermentation of carbohydrates (p. 154). In this manner ethyl alcohol may be prepared from glucose by fermentation with yeast.



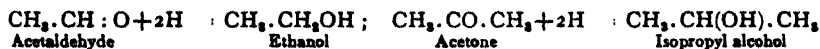
Similarly *n*-primary butyl alcohol is manufactured from starch by fermentation with *B. Clostridium acetobutylicum*.

(c) By the action of nitrous acid on primary amines the group NH_2 may be replaced by OH, and a primary alcohol formed. In some cases



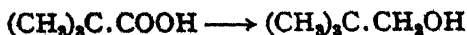
rearrangement occurs. Thus *n*-propylamine, $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$, yields with nitrous acid a mixture of *n*-propyl alcohol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$, and isopropyl alcohol, $(\text{CH}_3)_2\text{CH}\text{OH}$.

(d) A general method of preparing primary alcohols consists in the reduction of aldehydes, *e.g.* by use of sodium amalgam and very dilute mineral acid, or of zinc dust and acetic acid. In a similar manner ketones yield secondary alcohols.



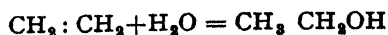
The reduction may be effected rapidly and in high yield by use of hydrogen in the presence of finely divided platinum or palladium at ordinary temperatures in a hydrogenation apparatus or by the Meerwein-Ponndorf method (p. 186).

Esters are reduced to alcohols by the use of sodium and alcohol (*Bouveault and Blanc* method). A much more effective reagent, however, is lithium aluminium hydride, a stable substance which in ether reduces many substances almost quantitatively at room temperature. Carboxylic acids or their esters are thus reduced to the corresponding primary alcohols, as exemplified by the preparation of neopentyl alcohol from trimethylacetic acid in 92 per cent. yield.¹



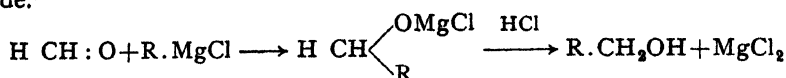
¹ R. F. Nystrom and W. G. Brown, *J.A.C.S.*, 1948, 90, 3738.

(e) A method of industrial importance is the hydration of olefin compounds. In the United States, for example, 65,000,000 gallons of ethyl alcohol are prepared each year from ethylene. For other details see pp. 151, 158, 159.

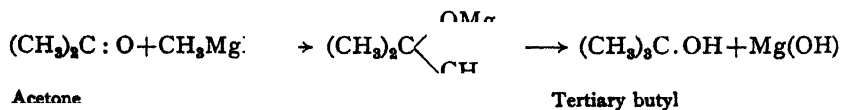
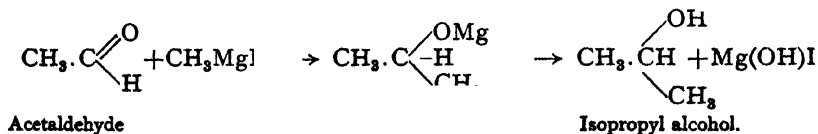


(f) Numerous syntheses of alcohols have been carried out by use of organomagnesium halides which unite with compounds containing a carbonyl group (such as aldehydes, ketones and esters) to form addition products which yield alcohols on being decomposed with ice and dilute acids.

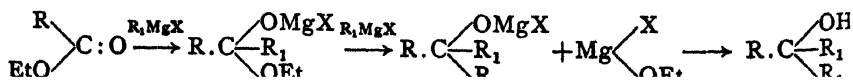
Primary alcohols are obtained by treating the reagent with formaldehyde.¹



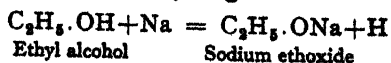
Secondary alcohols result from the interaction of alkyl magnesium halides with aldehydes or with formic esters, whereas *tertiary alcohols* are obtained from ketones and esters derived from higher homologues of



formic acid. In the last case addition of the reagent is followed by double decomposition in which the alkoxy group is exchanged for an alkyl radical.

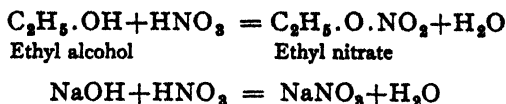


Chemical properties.—The chemical properties of the alcohols are associated with the functional group, the *hydroxyl group*, the hydrogen atom of which behaves very differently from that of the hydrogens in the alkyl radical, being directly replaceable by metals such as sodium and potassium, with evolution of hydrogen and formation of *alkoxides*.



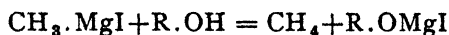
¹ The low yields often recorded for this reaction are said to be due to the production of formals, which can be readily decomposed by use of alcoholic hydrochloric acid to give 90 per cent. yields of the carbinols. N. Turkiewicz. *Ber.* 1920, 47, 2148.

Alcohols react with acids to form esters, *e.g.* ethyl nitrate.



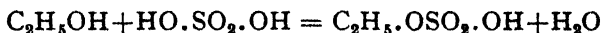
As already indicated, we may compare esters to the salts of inorganic chemistry, and the formation of esters from alcohols to that of salts from bases. The resemblance of the alcohols to the inorganic bases, however, is purely formal; the alcohols are neutral compounds and behave as such. The formation of a salt is an ionic reaction and proceeds instantaneously; whereas ester formation from acid and unionised alcohol progresses slowly.

The reactive nature of the hydrogen atom in the hydroxyl group is further shown by the interaction of alcohols with methyl magnesium iodide, when one molecule of methane is liberated for each hydroxyl group present:

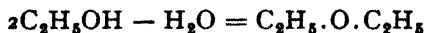


Since the methane so formed can be quantitatively estimated, the reaction is used to determine the number of hydroxyl groups in a compound (*Zerewitinoff* method).

Alcohols may be dehydrated in one of two ways. This is exemplified by the action of concentrated sulphuric acid on ethanol. At 80° the product is ethyl hydrogen sulphate.



At higher temperatures, however—140° and 180°—the products are diethyl ether and ethylene respectively.



Olefin formation occurs specially easily in the case of the tertiary alcohols.

The hydroxyl group may be replaced by halogen by treatment with phosphorus halides, alkyl halides being formed. Phosphorus pentachloride and ethanol, for example, give ethyl chloride, hydrogen chloride, and phosphorus oxychloride. Phosphorus



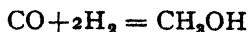
pentachloride may thus be used to detect the presence of the hydroxyl group in alcohols.

Primary, secondary and tertiary alcohols differ in their behaviour on oxidation and are thereby distinguished from one another (see beginning of this section). Their behaviour when led over reduced copper at 300°

Methyl alcohol, *methanol*, *carbinol* or *wood spirit*, CH_3OH , is found in the combined state in nature, *e.g.* in the form of methyl salicylate in oil of wintergreen, and as the methyl ester of anthranilic acid in oil of orange flowers.

It was long prepared technically by the dry distillation of wood at the lowest practicable temperature.

Since 1923 methyl alcohol has been synthesised industrially from the carbon monoxide of water gas (*Patart* Process, Badische Anilin und Soda Fabrik).

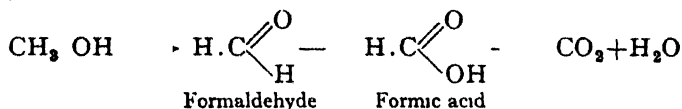


The reduction is effected by means of hydrogen at high temperatures (450°) and pressures (200 atmos.) in the presence of catalysts (zinc oxide and chromium oxide). Most of the methanol in the United States is now produced in this way. By varying the catalyst, *synthol*, a mixture of homologues of methanol, is produced.

Methyl alcohol is also prepared on the commercial scale by the catalytic oxidation of methane under a pressure of 100 atmospheres at 260° .



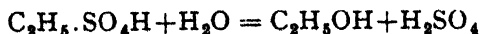
Pure methyl alcohol is an inflammable liquid of boiling-point 64.6° , which is miscible in all proportions with water. In chemical behaviour it strongly resembles ethyl alcohol. On mild oxidation it is converted into formaldehyde, which in turn may be further oxidised to formic acid and finally carbon dioxide.



Large quantities of methyl alcohol are used in the preparation of formaldehyde.

Ethyl alcohol, *ethanol*, *spirits of wine*, $\text{CH}_3\text{CH}_2\text{OH}$, is found occasionally in nature, *e.g.* as the butyric ester in unripe fruit of *heracleum giganteum* and in diabetic urine.

Ethyl alcohol is synthesised on the technical scale by hydrating ethylene. Ethylene is absorbed by sulphuric acid and the resulting ethyl hydrogen sulphate passed into water and heated to hydrolyse the ester to ethyl alcohol.



Ethyl alcohol prepared by this method is not contaminated by higher alcohols.

In America, Germany and probably other countries considerable quantities of alcohol are produced by the *Scholler process* in which sawdust is treated with dilute sulphuric acid under pressure and the resulting sugars fermented.

Alcoholic Fermentation. The other industrial source of ethanol is the fermentation process based on the decomposition of various sugars, particularly glucose, in the presence of living yeast cells. The main products are ethanol and carbon dioxide.



In addition to ethanol a number of by-products are formed which vary with the sugar employed and the conditions of fermentation. Prominent among these are the higher alcohols especially amyl alcohol, $\text{C}_5\text{H}_{11}\text{OH}$, succinic acid, acetaldehyde and glycerol.

The starting materials for the manufacture of ethanol are cheap substances from which glucose may be generated and subsequently fermented. They include starchy substances such as potatoes, corn, barley, rice; cellulose products; cane and beet sugar or the molasses obtained from their manufacture. Molasses have the advantage that they are directly fermentable, whereas starch and other polysaccharides are not fermented by yeast and must first be hydrolysed to fermentable sugars (see below).

The most representative production of ethanol is that in which starchy material forms the starting-point. Three separate stages may then be distinguished in the process. (1) Hydrolysis (*saccharification*) whereby the starchy raw is converted into sugar. (2) Decomposition of the sugar in the resulting liquid by fermentation. (3) Distillation of the alcoholic liquids from the fermented mash and final rectification of the distillate.



Stage I. Starch is converted by certain catalysts called *enzymes* (see p. 86o) into the sugar maltose, which under the influence of other enzymes present in yeast, is hydrolysed to glucose. Since maltose is also a fermentable sugar, we may consider the two monosaccharides maltose and glucose to be the immediate sources of ethanol. The breakdown of starch to maltose is usually brought about on the industrial scale by means of the enzyme *diastase*, a white colourless powder. Diastase is not employed in the pure form, but is used together with the whole corn as *malt*, which is preferably obtained by the germination of barley. The malt is mixed with water and unmalted corn, when the latter is transformed into sugar. The liquid or mash so obtained is then ready for fermentation.

Stage II. The sugar in the mash is then fermented by the addition of yeast, which contains the necessary enzymes, and the fermentation allowed to proceed at a temperature not higher than 33°. Fermentation of the mash occupies three to four days, and is accompanied by the evolution of carbon dioxide and consequent frothing of the liquid

Alcoholic fermentation, it may be noted, is an *anaerobic process*, i.e. occurs in the absence of air.

Stage III. From the fermented mash, in which the concentration of alcohol does not exceed 18 per cent., ethanol is removed by distillation. For this purpose stills are employed which permit the direct distillation of approximately 90 per cent. ethanol. The aqueous mass which remains behind in the distillation vessel is termed "spent wash", and is utilised as cattle food; in it are to be found nearly all the proteins contained in the starting material.

The raw spirit is next refined by rectification, at least four fractions being collected as follows:

1. Low-boiling by-products consisting mainly of acetaldehyde.
2. Spirit of 93 per cent. ethanol.
3. Spirit of 90 per cent. ethanol.
4. Final runnings, i.e. higher boiling products, containing amongst other substances amyl alcohols (*fusel oil*), which consists of a mixture of isomeric alcohols of the formula $C_5H_{11}OH$.

For the preparation of alcohol of higher purity than 93 per cent. purity fractions 2 and 3 are again submitted to fractional distillation in special apparatus, whereby ethanol containing 99.9 per cent. is obtained. Alcohol containing a small percentage (4 to 5) of water may also be rendered anhydrous by distillation over quicklime or barium hydroxide.

Very different views have been expressed as to the significance of the processes underlying alcoholic fermentation. Pasteur believed fermentation to be a purely physiological action, inseparably bound up with the life of the yeast cells and actuated by cellular metabolism.

Liebig, on the other hand, considered it to be a purely chemical change. The point was settled later by E. Buchner, who submitted a mixture of yeast and fine sand to strong pressure, disrupting the cell walls and obtaining an "expressed yeast juice" which no longer contained living cells, but nevertheless possessed strong fermentative power. This ability to induce fermentation was retained even after the liquid had been evaporated *in vacuo* and the dry mass again brought into solution.

The chemical changes taking place during fermentation are therefore due to the activity of this substance, named *zymase*, which belongs to the enzyme group, and has been shown by later investigations to be composed of a number of individual enzymes. The yeast cells only participate in the process of fermentation in so far as they generate zymase. Alcoholic fermentation may therefore be defined as the change brought about by the action of zymase on certain sugars.

Enzymes or unorganised ferments occur widely in plant and animal life and play an important part in metabolism. It is a characteristic property of the enzymes that each shows its activity towards either a definite chemical compound or a series of compounds with the same molecular structure. Emil Fischer, to whose work we owe much of our knowledge of these substances, compared the relationship between enzyme

and compound attacked to that between a key and its lock. This metaphor applies so completely that the enzyme does not even attack the stereoisomeride of the compound towards which it shows its activity. The selectivity is probably connected with the asymmetry of the enzyme molecule.

The mechanism of fermentation is discussed on p. 336.

Properties.—Ethyl alcohol is a colourless mobile liquid with a pleasant, pungent smell. It boils at 78.3° ; sp. gr. 0.789 at 20° . Alcohol burns with a pale blue non-luminous flame. It is extremely hygroscopic and mixes in all proportions with water, when a contraction in volume takes place. The greatest diminution occurs when 53.9 vols. alcohol are added to 49.8 vols. water, the mixture occupying 100 vols. instead of 103.7. The concentration of aqueous solutions of alcohol may be ascertained by determining the specific gravity by the use of suitable hydrometers. In technical work the concentration is usually quoted in percentage by volume, and in scientific work in percentage by weight.

Pure ethanol free from water cannot be obtained merely by fractional distillation although the boiling-points of the two substances (78° and 100° C.) are reasonably far apart. The reason for this is that a mixture of ethanol (96 per cent.) and water (4 per cent.) has a higher vapour pressure than pure water, ethanol, or any other mixture of the two. This *constant boiling mixture* in consequence has the lowest boiling-point and is the first to distill when aqueous ethanol is boiled. The resulting *rectified spirit* can be made absolute either by distillation over quicklime or by *azeotropic distillation*, i.e. by fractional distillation of the rectified spirit after benzene has been added. Ethanol (18.5 per cent.), benzene (74.1 per cent.), and water (7.4 per cent.) form a ternary mixture of minimum boiling-point (65°). After all the water has been removed by distillation at this temperature the boiling-point rises to 68° and a constant boiling fraction of ethanol (32.4 per cent.) and benzene (67.6 per cent.) comes over. Finally absolute ethanol remains and distills at 78.3° .

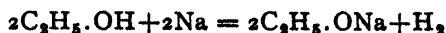
The percentage of ethanol in an aqueous alcohol mixture can be measured by its specific gravity. The standard spirit for excise duty purposes in Great Britain is called "proof" spirit and contains 57.1 per cent. of ethanol by volume. Alcoholic beverages are then assessed as *over* or *under* proof. For example, 100 volumes of a spirit "10° over proof" carries the same duty as 110 volumes of proof spirit. 100 volumes of a spirit "10° under proof" carries the same duty as 90 volumes of proof spirit.

Uses.—Alcohol is an excellent solvent for many organic compounds such as resins and oils. It is readily oxidised, being converted first into aldehyde and then into acetic acid. In addition to extensive use as a beverage, alcohol is employed for a variety of industrial and scientific purposes. Owing to its value as a solvent for resins and dye-stuffs it is required in quantity for the preparation of colourless and coloured varnishes. It enters into the production of a number of coal-tar dyes

alkaloids and other preparations such as perfumes and collodion. As the starting material it functions in the preparation of numerous organic compounds such as ether, chloroform, chloral and fulminates of mercury and silver. In scientific laboratories it is one of the commonest solvents and is also used as a source of heat.

Alcohol intended for use as a beverage is usually heavily taxed and therefore expensive. On the other hand, alcohol for industrial purposes is now duty free in most countries, including Great Britain, where for many years the tax very seriously affected the industry in fine chemicals. Industrial alcohol, however, must first be denatured or rendered unfit for human consumption by the addition of certain substances. The denaturants may be crude wood spirit and pyridine bases, as in Germany; a mixture of wood naphtha, mineral naphtha and pyridine as in Great Britain; or benzene and wood spirit as in America. In addition, incompletely denatured alcohol (industrial methylated spirits), or alcohol containing special denaturants, is allowed for use in those industries where ordinary methylated spirits would be unsuitable.

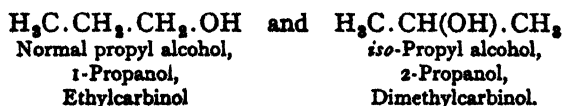
Sodium ethoxide, C_2H_5ONa , is obtained by dissolving sodium in excess of absolute alcohol:



It is readily soluble in alcohol, giving a solution which turns brown in air owing to oxidation. The pure compound forms a white powder and is frequently employed alone or in alcoholic solution as a condensing agent in organic synthesis.

Tribromoethyl alcohol, *Avertin*, $CBr_3.CH_2.OH$, is a white crystalline substance, m.p. 80° , which is used medicinally for inducing rectal narcosis.

Propyl alcohols, *propanols*, $C_3H_7.OH$. Both of the theoretically possible structural isomerides of this formula are known, viz. :—



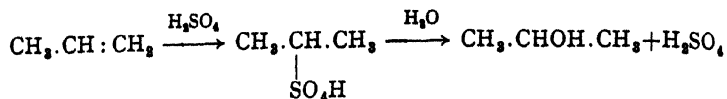
The constitution of both compounds follows from their behaviour on oxidation (see p. 147). Normal propyl alcohol on treatment with chromic acid is converted successively into propionaldehyde and propionic acid, showing it to be a primary alcohol; *iso*-propyl alcohol, on the other hand, yields acetone and is therefore a secondary alcohol.

Normal propyl alcohol, boiling-point 97° , sp. gr. 0.8044 at 20° , occurs in fusel oil, from which it is obtained by fractional distillation. In taste and smell it resembles ethyl alcohol.

iso-Propyl alcohol, b.p. 83° , is made on the commercial scale by catalytic reduction of acetone.



It is also made from propylene which is obtained in quantity in the U.S.A. by the "cracking" of petroleum hydrocarbons. Propylene hydrogen sulphate is obtained by absorption of propylene in sulphuric acid, and on hydrolysis gives *iso*-propyl alcohol.



Prepared in this way, *iso*-propyl alcohol is a source of acetone and ketene.

Butyl alcohols, $\text{C}_4\text{H}_9.\text{OH}$. Four structural isomerides are theoretically possible, all of which are known.

1. *n*-Butyl alcohol, *propylcarbinol*, $\text{CH}_3.\text{CH}_2.\text{CH}_2.\text{CH}_2\text{OH}$, can be prepared by reducing butyric aldehyde. It is obtained on the large scale by two processes.

Fermentation of grain, potatoes, or molasses with *B. Clostridium acetobutylicum* (Weizmann) gives three main products—*n*-butyl alcohol (60 parts), acetone (30 parts), and ethyl alcohol (10 parts). The alcohol is also made (U.S.A.) by the condensation of acetaldehyde to give aldol from which crotonaldehyde is obtained by dehydration. Hydrogenation of the unsaturated aldehyde gives *n*-butyl alcohol.

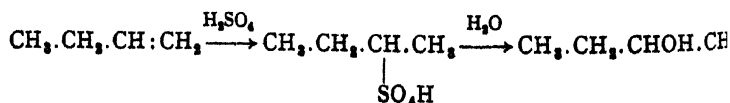


It is a colourless liquid, b.p. 117° , with a smell both of alcohol and fusel oil

2. Secondary butyl alcohol, *methylethylcarbinol*, $\text{C}_4\text{H}_9.\text{CHOH}.\text{CH}_3$, is best prepared by the reduction of methyl ethyl ketone.



It is manufactured (U.S.A.) by the hydration of butylene (*cf.* preparation of *iso*-propyl alcohol).

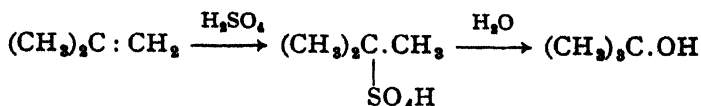


Secondary butyl alcohol is a colourless, pleasant-smelling liquid, b.p. 98°

3. Isobutyl alcohol, *fermentation butyl alcohol*, *isopropyl-carbinol*, $(\text{CH}_3)_2\text{CH}.\text{CH}_2\text{OH}$, is formed in small amount during the alcohol fermentation of sugar. It is also obtained as a side-product in the manufacture of synthetic methyl alcohol from carbon monoxide and hydrogen or from fusel oil. It readily undergoes rearrangement; for example, the main product with hydrobromic acid is *tert*-butyl bromide.



4. Tertiary butyl alcohol, *trimethylcarbinol*, melts at 25°. It is manufactured by hydration of *isobutylene*.



A number of butyl esters are valuable commercially : for instance, butyl acetate is a good solvent, butyl methacrylate an excellent optical adhesive, and dibutyl phthalate a useful mosquito and midge repellent.

Amyl alcohols, $\text{C}_5\text{H}_{11}\text{OH}$, should exist according to theory in eight isomers. All of these are known. .

1. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2\text{OH}$, normal amyl alcohol, b.p. 138°.
2. $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2\text{OH}$, fermentation amyl alcohol, b.p. 131°.
3. $\text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2\text{OH}$, usually known as active amyl alcohol, b.p. 128°.
4. $(\text{CH}_3)_3\text{C} \cdot \text{CH}_2\text{OH}$, tertiary butyl-carbinol, b.p. 112°.
5. $(\text{C}_2\text{H}_5)_2\text{CHOH}$, diethylcarbinol, b.p. 117°.
6. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} \begin{matrix} \text{CH}_3 \text{ CH}_2 \\ \diagup \quad \diagdown \end{matrix} \text{CHOH}$, methyl-*n*-propylcarbinol, b.p. 120°.
7. $(\text{CH}_3)_2\text{CH} \begin{matrix} \text{CH}_3 \\ \diagup \end{matrix} \text{CHOH}$, methyl-*iso*propylcarbinol, b.p. 114°.
8. $\text{CH}_3\text{CH}_2 \begin{matrix} \text{CH}_3 \\ \diagup \end{matrix} \text{C}(\text{OH}) \cdot$, dimethyl-ethylcarbinol, b.p. 102°.

Amyl alcohols are now prepared commercially by the chlorination of pentanes obtained from natural gas. The following products are obtained :—

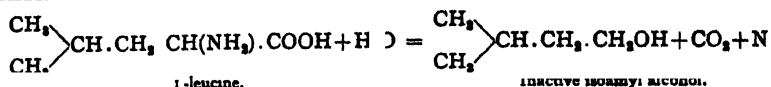
1. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2\text{Cl}$. . .	24 per cent
2. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHCl} \cdot \text{CH}_3$. . .	8 "
3. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CHCl} \cdot \text{CH}_2 \cdot \text{CH}_3$. . .	18 "
4. $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2\text{Cl}$. . .	15 "
5. $(\text{CH}_3)_2\text{CCl} \cdot \text{CH}_2 \cdot \text{CH}_3$. . .	5 "
6. $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{CH}_2\text{Cl}$. . .	30 "

Hydrolysis gives the corresponding alcohols.

Another source of amyl alcohols is fusel oil.

Fermentation amyl alcohol, *isoamyl alcohol*, $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2\text{OH}$, is the chief constituent of fusel oil—an oil formed in comparatively small quantities in alcoholic fermentation processes. F. Ehrlich showed that the production of fusel oil during fermentation is a result of the protein-forming activity of the living yeast cells and is due to the disruption of certain amino-acids, particularly leucine, isoleucine and valine, by the yeast to satisfy its need for nitrogen and for the production of zymase. The corresponding higher alcohols are left behind as non-assimilable

products of metabolism. In this way L-leucine gives rise to inactive isoamyl alcohol, L-isoleucine to laevorotatory amyl alcohol, and valine to isobutyl alcohol.



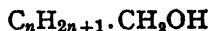
Fermentation amyl alcohol is always accompanied by active amyl alcohol, 2-methyl-1-butanol, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}(\text{CH}_3) \cdot \text{CH}_2\text{OH}$, which is of interest as one of the simplest examples of an optically active compound.

Dimethylethylcarbinol, *tertiary amyl alcohol*, *amylen hydrate* $(\text{CH}_3)_2\text{C}(\text{OH}) \cdot \text{C}_2\text{H}_5$, is a liquid with a smell like camphor. It is used as a hypnotic and is prepared industrially from fermentation amyl alcohol. When the latter is dehydrated a mixture of isomeric amylenes is obtained among which is *trimethylethylene*, a narcotic (*pental*). Trimethylethylene by the action of sulphuric acid and water is converted into tertiary amyl alcohol (*cf.* preparation of *isopropyl alcohol*).



Higher alcohols. Among the higher alcohols may be mentioned *octyl alcohol*, now prepared on the commercial scale, *cetyl alcohol* $\text{C}_{16}\text{H}_{33}\text{OH}$, and *melissyl alcohol*, $\text{C}_{30}\text{H}_{61}\text{OH}$, both of which are present in waxes.

Recently a number of alcohols of the general formula



where n may be any odd number between 7 and 17 have been prepared industrially by the catalytic reduction of fatty acids according to the equation :



The resulting so-called *fatty alcohols* such as lauryl and myristyl alcohols are useful commercial commodities. For example, on sulphonation detergent and wetting products are obtained, while blending with fatty acids gives waxes with desirable properties.

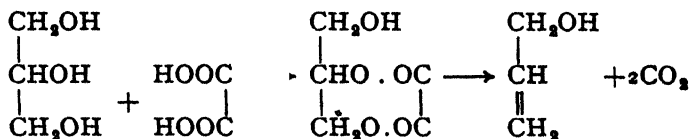
UNSATURATED MONOHYDRIC ALCOHOLS

These may be derived from the olefins or acetylenes, and consequently show on the one hand the behaviour typical of the saturated alcohols, and on the other the additive properties of the unsaturated hydrocarbons.

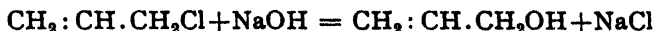
It should be remembered that the grouping : $\text{C} : \text{CH} \cdot \text{OH}$ is unstable and readily passes over into the group : $\text{CH} \cdot \text{CH} : \text{O}$; *i.e.* the alcohols in which the hydroxyl group is attached to a doubly bound carbon atom are for the most part unstable and isomerise into the corresponding aldehydes. An example of this type is *vinyl alcohol*, ethenol, $\text{CH}_2 : \text{CH} \cdot \text{OH}$, traces of which are supposed to be present in commercial ether.

This alcohol is not known in the pure state, but has been found to occur as an intermediate in the slow oxidation of ethylene, under which conditions it exists in equilibrium with its two isomerides ethylene oxide and acetaldehyde.¹ Vinyl alcohol may be isolated from this mixture in the form of its double compound with mercury oxychloride.

On the other hand, unsaturated alcohols in which the hydroxyl group is united to a singly bound carbon atom are stable and are known in large number. One of the most important of these is **allyl alcohol**,



-propenol, $\text{CH}_2 : \text{CH} \cdot \text{CH}_2\text{OH}$, which occurs in raw wood spirit (0.1 to 2 per cent.). It is prepared by heating glycerol with oxalic acid at 60° . Chattaway showed that a neutral glyceryl oxalate is first formed and this is decomposed by heat into allyl alcohol and carbon dioxide. It is manufactured by the hydrolysis of allyl chloride, which is easily obtained by the chlorination of propylene (p. 139).

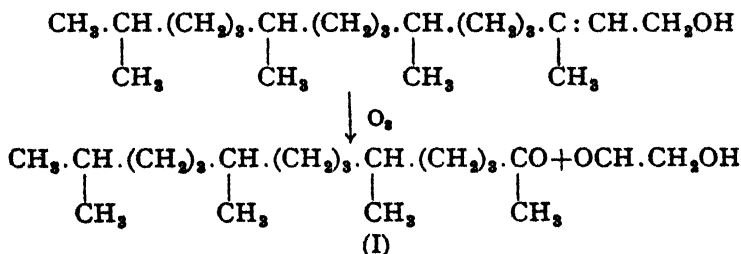


When oxidised under certain conditions it yields first acrylyc aldehyde or acrolein and then acrylyc acid.



Allyl alcohol is a pungent-smelling liquid, b.p. 96° .

Phytol, $\text{C}_{20}\text{H}_{39}\text{OH}$, is one of the higher unsaturated alcohols. It possesses special interest as standing in close relationship to chlorophyll (the green colouring matter of leaves), from which it was isolated by Willstätter. Phytol is a colourless oil, which cannot be distilled without decomposition except at extremely low pressures. It boils at 145° under 0.3 mm. pressure, and has the following structure²:



Its structure has been determined by synthesis and ozonolysis which gives the ketone (I) and glycollic aldehyde.

Examples of other unsaturated alcohols will be found in the section on terpenes.

¹ D. M. Newitt, see W. A. Bone, *J.*, 1933, 1604.

² F. G. Fischer and K. Löwenberg,

Ann., 1928, 454, 69; 1929, 475, 183.

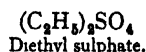
V

Esters of Monohydric Alcohols with Inorganic Acids

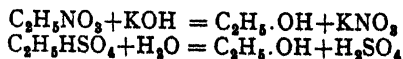
As already mentioned on p. 134, *esters* may be compared to metallic salts, and are produced by the union of acids and alcohols with simultaneous liberation of water. Corresponding to halide salts are the esters of halogen acids, already treated on p. 133 under the heading of monohalogen substitution products of the hydrocarbons. Esters are also known of other mineral acids. Polybasic acids give rise to several series of esters in the same manner as they form several series of salts.

When the total replaceable hydrogen of an acid is displaced by alkyl groups, neutral esters are formed, corresponding to neutral salts. These esters are mostly liquids of neutral reaction, often of very pleasant odour and almost or completely insoluble in water.

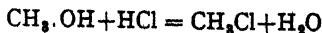
If, on the other hand, the replaceable hydrogen of a polybasic acid is incompletely substituted by alkyl groups, an *acid ester* or ester-acid is produced. Acid esters are genuine acids and capable of exchanging the as yet unreplaced hydrogen for metals in the usual manner. They are considerably less stable than the normal esters, are odourless and generally dissolve readily in water.



Esters are *hydrolysed* on heating with sodium or potassium hydroxide, or by treatment with superheated steam, when they break up into the alcohol and acid from which they are derived. The former process has long been employed in the manufacture of soaps from fats and is therefore known as **saponification**. Acid esters are often hydrolysed to the free acid and alcohol merely on being mixed with water at the ordinary temperature, but the action occurs more readily on boiling.



Methods of Formation.—1. Frequently by direct interaction of acid and alcohol.



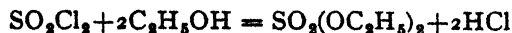
Under these conditions polybasic acids first give rise to the acid esters.

In this case there is no quantitative conversion of alcohol and acid into ester, but the formation of the latter ceases at a certain point. This state of affairs is brought about by the hydrolytic action of the water liberated, and leads eventually to a state of equilibrium. By employing an excess of acid or by removing the ester from the reaction mixture (*e.g.* by continuous distillation) a larger yield may be attained.

2. By the action of silver salts of the acids on alkyl halides.¹



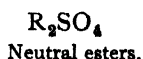
3. By double decomposition between acid chlorides and alcohols or preferably sodium alcoholates.



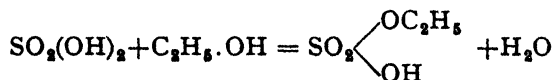
Among the numerous esters of mineral acids the most interesting are those of sulphuric acid.

Esters of Sulphuric Acid

Sulphuric acid gives rise to two types of esters—*acid esters* and *neutral esters*.



Acid esters of sulphuric acid, RHSO_4 , usually termed alkyl hydrogen sulphates, are produced on mixing alcohols with concentrated sulphuric acid or by the union of ethylene hydrocarbons with concentrated sulphuric acid (p. 123).

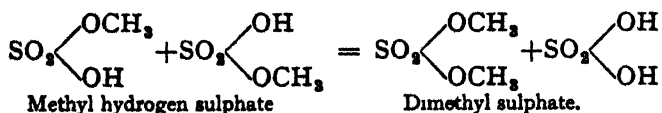


They possess a strong acid reaction, and their salts are, for the most part, readily soluble in water. Among the latter the alkali salts crystallise well, and are used in a variety of reactions. For example, ethyl bromide is conveniently prepared by the dry distillation of a mixture of potassium ethyl sulphate and potassium bromide.

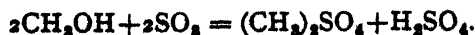


The alkali salts yield mercaptans when heated with potassium hydrosulphide, thio-ethers with potassium sulphide, and alkyl cyanides with potassium cyanide.

Neutral esters of sulphuric acid, R_2SO_4 , are produced by the distillation of alkyl sulphuric acids, by heating alcohols with sulphuric acid or sulphuryl chloride, or alkyl iodides with silver sulphate. The most important neutral ester is dimethyl sulphate, which is used industrially



and in the laboratory as a methylating agent. It may be prepared by the decomposition of methyl hydrogen sulphate by distillation at a high temperature, or by adding the required amount of sulphur trioxide to cooled methyl alcohol,



¹ Sometimes an isomeric ester of the expected ester is obtained by this method.

It is prepared commercially by the distillation of methyl alcohol and fuming sulphuric acid *in vacuo*.

Dimethyl sulphate boils at 188°, strongly attacks the mucous membranes and is poisonous. It is a valuable methylating agent and may be substituted in all cases for methyl iodide, although under the usual experimental conditions only one of the two methyl groups is utilised. In general it reacts with much greater rapidity and gives better yields than methyl iodide. It is especially effective for the methylation of phenols and carbohydrates.

Diethyl sulphate is used in the manufacture of ethyl-cellulose and is obtained by the action of sulphuric acid on ethyl alcohol. Like dimethyl sulphate it is poisonous.

Esters of nitric acid are produced by the action of alcohols on concentrated nitric acid, free from oxides of nitrogen. They are mobile liquids which are practically insoluble in water, and explode when rapidly heated.

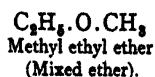
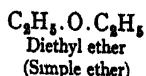
The **esters of nitrous acid**, $R \cdot O \cdot NO$, are isomeric with the nitro-paraffins, $R \cdot NO_2$, and of these only the isoamyl ester, $C_5H_{11} \cdot O \cdot NO$, usually known as *amyl nitrite*, need be mentioned. It is prepared by leading nitrogen trioxide into hot amyl alcohol, and is a yellow liquid, b.p. 98°. It is employed in medicine (*amyl nitris*) on account of its property of expanding the blood vessels and relaxing the contractile muscles.

Among less common inorganic esters, those of phosphoric acid are of great importance in the investigation of naturally occurring phosphorus compounds of physiological importance (see nucleic acids).

VI

Ethers

Ethers may be considered to be anhydrides of the alcohols in the same way as metallic oxides are anhydrides of the corresponding hydroxides. According to whether the alkyl radicals united to the oxygen atom are similar or dissimilar, the compounds are known as *simple* or *mixed ethers*.



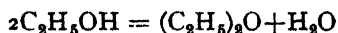
They may be prepared :

1. By the interaction of sodium alkoxides with alkyl halides in alcoholic solution. By this synthesis the structure of the ethers was first



established by Williamson.

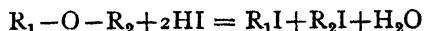
2. By the dehydration of alcohols (*cf.* p. 151). This is usually effected by heating alcohol with concentrated sulphuric acid at 140° (see below). This method of formation is of great practical importance,



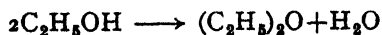
although it only gives satisfactory yields up to dipropyl ether. With higher alcohols water tends to split off to form unsaturated hydrocarbons of the ethylene series.

3. Dehydration may also be effected by utilising the catalytic effect of certain metallic oxides (Sabatier and Maihle). If the vapour of ethyl alcohol is led over precipitated alumina at temperatures between 240° and 260° , the dehydration of the alcohol does not result in the formation of ethylene, $\text{C}_2\text{H}_5\text{OH} = \text{H}_2\text{O} + \text{C}_2\text{H}_4$, but yields ether. Methyl ether, $\text{CH}_3\cdot\text{O}\cdot\text{CH}_3$, is obtained even more readily under these conditions, since the formation of an ethylene hydrocarbon is not possible in this case.

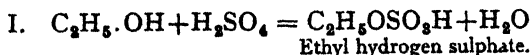
Ethers are very mobile liquids of neutral reaction and are only sparingly soluble in water. Chemically they are inert; they are not attacked by metals such as sodium and the ether linkage, $\text{C}-\text{O}-\text{C}$, is not readily broken except by reagents such as boiling hydriodic acid, boron trifluoride, or aluminium chloride.



Ether, ethyl ether, $(\text{C}_2\text{H}_5)_2\text{O}$, is by far the best known and most important compound of this series. It is prepared technically and in the laboratory by heating a mixture of nine parts of concentrated sulphuric acid and five parts of 90 per cent. alcohol to a temperature of 135° to 140° . Ether and water distil over, and a continuous supply



of alcohol is allowed to flow into the distillation vessel, where it is immediately acted upon by the sulphuric acid. The course of the reaction was explained by Williamson by the following equations:



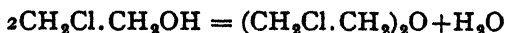
Hence it would be expected that small amounts of sulphuric acid should be capable of converting unlimited quantities of alcohol into ether. In practice, however, this cannot be realised, owing to dilution of the acid by the liberated water and the incidence of by-reactions.

Van Alphen¹ has shown that Williamson's theory of ether formation in the presence of sulphuric acid must be modified in the light of further research. Ethyl alcohol may be converted into ether by heating it with any acid which is of sufficient strength, *e.g.* arsenic, phosphoric, sulphurous, picric and chloracetic acids, as well as benzene sulphonic acid, hydrochloric acid and hydriodic acid. Many salts of weak organic and inorganic

¹ J. van Alphen, *Rec. Trav. Chim.*, 1930, 49, 756.

Ether when exposed to atmospheric oxygen for a long time is oxidised and is then found to contain peroxides. Ether which contains peroxides is liable to explode on distillation.

β : β' -Dichloroethyl ether, $(\text{CH}_2\text{Cl}.\text{CH}_2)_2\text{O}$, is obtained on the commercial scale by the dehydration of ethylene chlorhydrin.



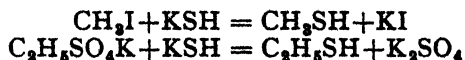
It is an excellent solvent and is used for removing olefinic and aromatic components from lubricating oils.

VII

Thio-alcohols and Thio-ethers

If the oxygen in an alcohol is replaced by sulphur, the resulting compound is known as a **thio-alcohol**, **mercaptan**. An example of this type is CH_3SH , methyl mercaptan. As may be seen from their properties, these compounds bear the same relation to hydrogen sulphide as the alcohols to water. While in some respects resembling the alcohols they exhibit weak acidic properties, as would be expected from their derivation from hydrogen sulphide. Characteristic of thiol derivatives are the water-insoluble compounds formed by the action of mercury, silver and copper (cuprous) ions, the hydrogen of the $-\text{SH}$ group being replaced by metal. Hence the name mercaptan (*mercurium aptans*). With mineral acids the metallic derivatives or mercaptides regenerate the free mercaptan. It should be noted that the alcohols form salts only with the alkali metals.

Mercaptans may be obtained by warming alkyl halides or salts of an alkylsulphuric acid with potassium hydrosulphide,



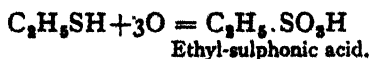
and by the action of phosphorus pentasulphide on alcohols,



Mercaptans have an extremely nauseous smell and boil at much lower temperatures than the corresponding alcohols. Like hydrogen sulphide they are readily attacked by oxidising agents. For example, under the influence of atmospheric oxygen they are converted into disulphides.

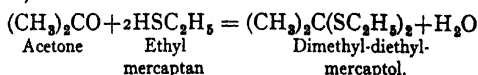


Nitric acid transforms them into sulphonc acids



Ethyl mercaptan, C_2H_5SH , commonly known as *mercaptan*, is the most important representative of this class. It is obtained technically from ethyl chloride and potassium hydrosulphide, and is used in the preparation of sulphonal. Ethyl mercaptan is a particularly evil-smelling liquid of boiling-point 36° . It dissolves sparingly in water, and in air rapidly oxidises to ethyl disulphide, $(C_2H_5)_2S_2$.

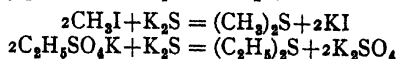
Mercaptan condenses with acetone with elimination of water according to the equation,



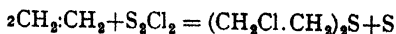
When the product of condensation is oxidised with potassium permanganate it yields diethylsulphone-dimethylmethane (acetone-diethylsulphone), $(CH_3)_2C(SO_2C_2H_5)_2$, which is employed as a hypnotic under the name of **sulphonal**.

Trional, $\begin{array}{c} CH_3 \\ \diagup \\ C_2H_5 \end{array} C(SO_2C_2H_5)_2$, is prepared in a corresponding manner to the above and possesses similar properties.

Thio-ethers or *alkyl sulphides*, such as methyl sulphide, $(CH_3)_2S$, are formed by heating potassium sulphide, K_2S , with an alkyl iodide.

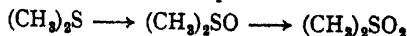


$\beta\beta'$ -*Dichloroethyl sulphide* (*Mustard gas*), $(ClCH_2.CH_2)_2S$, has been used as a poison gas in warfare, and among other methods may be prepared by the following reaction :



Thio-ethers are neutral volatile liquids of nauseous smell. With metallic salts they yield double compounds of the type $(C_2H_5)_2S.HgCl_2$.

With mild oxidising agents one atom of oxygen is taken up to form *sulphoxides*. Under more vigorous oxidation two atoms of oxygen enter the molecule with the formation of *sulphones*.



There has been considerable discussion as to the nature of the sulphur-oxygen. The lengths of the sulphur-oxygen bonds in dimethyl sulphone and thionyl chloride are 1.46 Å and 1.45 Å respectively, both of which are not only shorter than the calculated S-O length (1.70 Å) but are also shorter than the calculated S = O length (1.49 Å). The dipole moment of a S→O bond might have a maximum value of 6.86 D, but the observed value is 2.16-2.6, i.e. only 31.5-38 per cent. of the theoretical. These and other data have led Phillips, Hunter, and Sutton¹ to regard the sulphur-oxygen bond in sulphoxides, etc., as simple double bonds and not co-ordinate linkages. Further evidence to support this conclusion is desirable (see A. F. Wells, *J.*, 1949, 55).

¹ G. M. Phillips, J. S. Hunter, and L. E. Sutton, *J.*, 1945, 146. Cf. M. M. Jamieson, M. S. Leslie, and E. E. Turner, *Ann. Reports*, 1946, 43, 156.

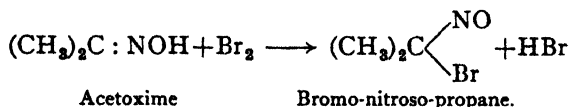
VIII

Alkyl Nitrogen Compounds

I.—NITROSO-DERIVATIVES

Nitroso-compounds are those in which the *nitroso group* —N : O is united to a hydrocarbon radical. They must not be confused with the *isonitroso-compounds* or *oximes* which contain the *isonitroso-* or *oximino-group*, : NOH. They may be obtained by the following methods :—

1. By treating oximes with an oxidising agent such as bromine dissolved in pyridine, or chlorine in hydrochloric acid. The change occurs with greater ease when the carbon atom attached to the nitrogen simultaneously passes over into the tertiary condition. For instance, the reaction between acetoxime and bromine proceeds according to the equation,



2. By oxidising an amine containing a tertiary carbon atom with Caro's acid (monopersulphuric acid). In this manner tertiary nitroso-butane is obtained from tertiary butylamine.

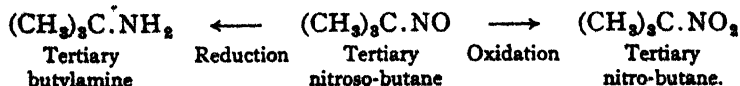


3. Nitroso-compounds containing other substituents in the molecule in addition to the nitroso group are formed by the action of nitrogen peroxide, nitrogen trioxide, nitrosyl chloride or nitrosyl bromide on ethylene hydrocarbons (see p. 392).

Properties.—True nitroso-compounds can exist in two modifications, one of which is dimolecular, colourless and solid, and the other monomolecular, blue and often liquid. The typical nitroso-derivatives are monomolecular liquids or crystalline solids of deep blue colour. They are highly volatile and have a characteristic and usually pungent smell. The colourless crystalline dimolecular forms give blue oils on fusion, and under suitable conditions dissolve with the production of a blue solution.

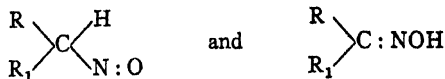
Nitroso-butane, $(\text{CH}_3)_3\text{C.NO}$, for example, exists as a blue compound of the formula $\text{C}_4\text{H}_9\text{NO}$, and as a colourless modification of the formula $\text{C}_8\text{H}_{18}\text{N}_2\text{O}_2$. In solution, the latter undergoes partial dissociation, which increases with rise of temperature.

Nitroso-compounds may be oxidised to nitro-compounds and reduced to amines,



The majority of them give Liebermann's nitroso reaction (see p. 178).

Isomerism of nitroso-compounds.—It has been shown that aliphatic nitroso-compounds exhibit tautomerism as expressed in the formulæ

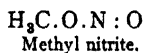
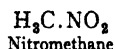


Thus the blue monochloro-nitroso-ethane readily changes into the isomeric oxime on standing at the ordinary temperature in ethereal solution.



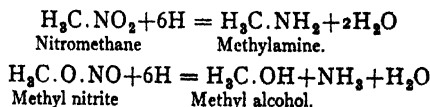
II.—NITRO-COMPOUNDS¹

Nitro-derivatives of the hydrocarbons are those in which hydrogen has been replaced by the monovalent nitro group —NO_2 . It should be noted that certain nitric acid esters prepared on a technical scale, such as nitro-glycerine and nitro-cellulose, are also frequently but incorrectly termed nitro-compounds. In all true nitro-compounds nitrogen is united directly to carbon, whereas in the isomeric nitrites (p. 164) it is linked indirectly through oxygen to the alkyl group.



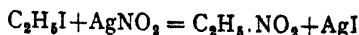
This difference of constitution may be deduced more particularly from the following two reactions :—

1. On reduction nitro-compounds are converted into amino-compounds. Under the same conditions nitrites yield an alcohol and ammonia.



2. Nitro-derivatives of the hydrocarbons are not decomposed by the action of alkalis; nitrous acid esters, on the other hand, are hydrolysed to give an alkali nitrite and the corresponding alcohol.

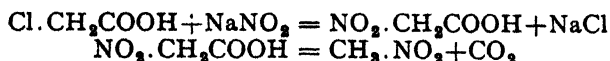
Nitro-compounds are prepared by the interaction of silver nitrite and an alkyl iodide (V. Meyer),



the corresponding alkyl nitrites being formed at the same time. Since the isomers differ considerably in boiling-point they may be separated by fractional distillation. Mercurous nitrite can be substituted for silver nitrite in the above reaction.

¹ For a general review see N. Levy and J. D. Rose, *Chemical Society Quarterly Reviews* 1948, 1, 358.

Nitro-paraffins are frequently prepared from the α -halogen-substituted fatty acids. On treatment with sodium nitrite these yield α -nitro-substituted fatty acids, which readily lose carbon dioxide to give nitro-paraffins. In this manner nitromethane may be obtained from chloracetic acid and sodium nitrite :



In many cases it is also possible to prepare nitro-paraffins by heating the parent hydrocarbon with dilute nitric acid.

None of the above methods is satisfactory. The Victor Meyer method yields the isomeric nitrites as well as the nitro-compounds and the yields are frequently poor, while direct nitration of the paraffins is invariably accompanied by oxidation and formation of polynitro-compounds. In consequence, the nitroparaffins have hitherto belonged to the "rare chemical" class. Recently, however, nitroparaffins have come on the market at reasonable cost, thanks to the researches of H. B. Hass, E. B. Hodge and B. M. Vanderbilt¹ at Purdue University, U.S.A., which showed that nitric acid and paraffins react extremely rapidly in the gaseous phase at 400° C. - 450° C. to give good yields of nitroparaffins. For example, propane which occurs in abundance in natural gas and petroleum yields nitromethane, nitroethane, 1-nitropropane and 2-nitropropane.

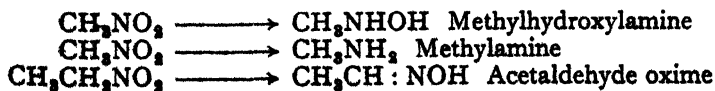


These nitroparaffins are now manufactured in the U.S.A. by this method.¹ As a result the price of nitroethane is now one-hundredth of the former figure.

It will be noticed that the products obtained are due not only to direct nitration but also to fission of the molecule with the production of nitromethane and nitroethane.

Nitromethane is not so readily nitrated as propane; ethane is somewhat more easily nitrated than methane and little difference is shown by the higher members of the series.

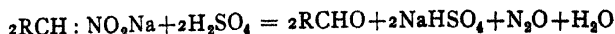
The nitroparaffins have many uses.² They are excellent solvents for cellulose esters, synthetic resins, etc., and are chemically extremely reactive, giving many valuable products. They may be reduced to substituted hydroxylamines, oximes, and amines.



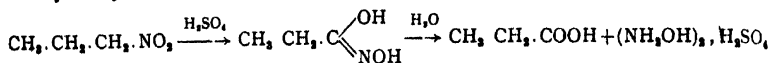
¹ H. B. Hass and E. F. Riley, *Chem. Rev.*, 1943, 32, 373.
Chem., 1940, 32, 887.

² C. L. Gabriel, *Ind. Eng.*

Aldehydes and ketones may also be prepared from the *aci*-nitro-paraffins (see below) with strong mineral acids.



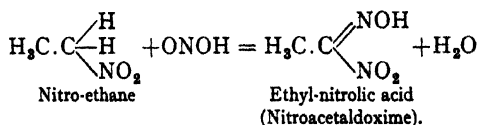
Finally, the action of strong mineral acids on the nitroparaffins may be mentioned. The products in this case are carboxylic acids and hydroxylamine salts. This is an excellent method for the preparation of hydroxylamine.



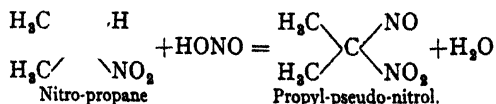
In addition to those already mentioned above, the following *properties and reactions of the nitro-paraffins* are of importance. They are colourless, pleasant-smelling liquids, sparingly soluble in water, which distil without decomposition and boil at a much higher temperature than the corresponding isomeric esters of nitrous acid.

The *behaviour of the nitro-paraffins towards nitrous acid* is very characteristic, and differs according as the compound is primary, secondary or tertiary. It thus serves as a means of distinguishing between these three types.

With a primary nitro-compound a **nitrolic acid**¹ is obtained, which dissolves in alkalis forming a metallic derivative and giving a blood-red coloration.



Secondary nitro-paraffins yield **pseudo-nitrols**, which are to be regarded as nitro-nitroso-compounds. They exist accordingly in two

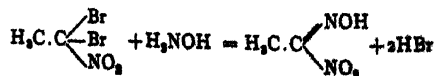


modifications (see p. 169), are colourless in the solid state and on fusion or in solution develop an intense blue colour.

Tertiary nitro-compounds do not interact with nitrous acid.

Nitro-olefins are also known. Nitroethylene, $\text{CH}_2:\text{CH}\cdot\text{NO}_2$, is prepared by the dehydration of 2-nitroethanol by phthalic anhydride. The nitro-olefins are useful preparative reagents.

¹ The constitution of **nitrolic acids** is shown by their formation from dibromo-nitro-paraffins and hydroxylamine.



Pseudo-acids

Those nitro-compounds in which at least one hydrogen atom is attached to the carbon atom binding the nitro group, *i.e.* primary and secondary nitro-compounds, are acidic in character.



Nitroethane
(primary)

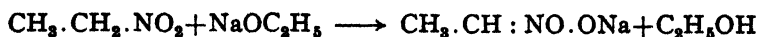


2-Methyl-2-nitroethane
(secondary)



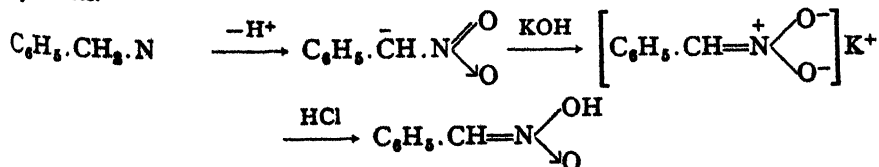
Tertiary nitrobutane

In such compounds one of the hydrogen atoms in the α -position can be replaced by sodium or potassium. The sodium derivatives are obtained by mixing the nitro-compounds with sodium ethoxide or methoxide in alcoholic solution, salt formation being accompanied by simultaneous or preliminary rearrangement of the NO_2 group into the $=\text{NO} \cdot \text{OH}$ group.



The salts are therefore not derived from nitro-paraffins but from labile isomerides known as **isonitroso-paraffins**. Following a suggestion of Hantzsch, the latter are distinguished as the *aci*-forms and the true nitro-compounds as **pseudo-acids**, the term pseudo or the Greek symbol *Psi* (ψ) being frequently used in organic chemistry to differentiate pairs of isomerides.

Much of our knowledge of the structure of the nitro-compounds and their salts comes from Hantzsch's investigations on phenylnitromethane. This is a true nitro-compound and not a nitrite since it is not easily hydrolysed and on reduction yields benzylamine. It is a colourless oily liquid which dissolves slowly in alkali to give a salt. Careful acidification in the cold with hydrochloric acid gives a second form, *aci*-phenylnitromethane, a crystalline solid, m.p. 84° . It is a hydroxy-compound since it gives a red-brown colour with ferric chloride, dissolves immediately in sodium hydroxide, reacts with phenyl isocyanate or phosphorus pentachloride, and liberates methane from methyl magnesium iodide (*Zerewitinoff test*). In contrast phenylnitromethane does not respond to any of these tests though it dissolves slowly in alkali as already mentioned. The formation of the *aci*-form is probably brought about by removal of a proton from the phenylnitromethane followed by electronic rearrangement to give a salt of the formula shown below. Acidification then gives the *aci*-compound (or **nitronic acid**), which gradually reverts to the oily form.

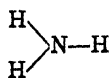


Phenylnitromethane is termed a pseudo-acid because it is not itself neutralised by alkali, but undergoes rearrangement first to the *aci*-form

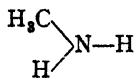
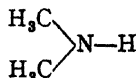
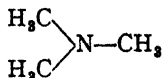
which then neutralises the alkali. Since this rearrangement is slow, neutralisation is slow. The formulæ above in addition to explaining the different chemical properties of the two forms also explain the different physical properties. Whereas phenylnitromethane is stable, neutral, and a non-conductor of electricity, the *aci*-form changes back to the nitro-form, is acidic, and conducts electricity. The absorption spectra of the two forms are also different and such differences often provide criteria for the presence of pseudo-acids.

III.—AMINES

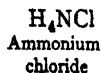
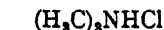
The hydrogen atoms of ammonia may be successively exchanged for alkyl groups with the formation of compounds known as amines or amine bases. According as one, two or three hydrogen atoms are replaced the resulting derivatives are described as *primary*, *secondary* or *tertiary amines* respectively. Primary amines contain the *amino*-group, —NH_2 , and secondary amines the *imino*-group, =NH .



Ammonia

Methylamine
(primary amine)Dimethylamine
(secondary amine)Trimethylamine
(tertiary amine)

All three classes of amines resemble ammonia in possessing basic properties, and like the latter combine directly with acids to form salts in which the originally trivalent nitrogen changes into the pentavalent state. Tertiary amines also combine with alkyl halides to form quaternary ammonium salts, which may be regarded as ammonium halides in which all four hydrogen atoms are displaced by alkyl groups. Corresponding to these salts are the *quaternary ammonium hydroxides* of strongly basic character, closely approximating to potassium and sodium hydroxides in their behaviour.

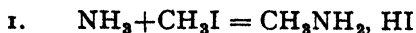
Ammonium
chlorideTrimethyl ammonium
chloride, or trimethyl-
amine hydrochlorideTetramethyl-
ammonium chlorideTetramethyl
ammonium hydroxide
(a quaternary base)

Quaternary ammonium compounds.

As will readily be understood, the amines present various possibilities of isomerism. We may meet with metamerism, as in the case of trimethylamine, $(\text{CH}_3)_3\text{N}$, methyl-ethyl-amine, $(\text{CH}_3)(\text{C}_2\text{H}_5)\text{NH}$, and propylamine, $\text{C}_3\text{H}_7\text{NH}_2$; with chain isomerism, dependent on the different mode of linking of the carbon atoms in the alkyl groups, and which may therefore appear in the case of a single group of three carbon atoms, *e.g.* propyl-amine, $\text{CH}_3\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$, and isopropyl-amine, $(\text{CH}_3)_2\text{CH}\cdot\text{NH}_2$; and finally, if alkyl groups containing a greater number of carbon atoms are present, with position isomerism caused by the varying position of the nitrogen in one and the same carbon chain.

Formation of Amines

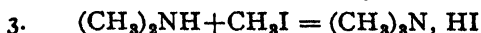
1. *Alkylation Methods*.—It was discovered by Hofmann that the hydrogen of ammonia is readily replaced by alkyl groups when an aqueous or alcoholic solution of ammonia is heated with *alkyl halides*. An atom of halogen first unites with a hydrogen atom of ammonia to form hydrogen halide, the place of the hydrogen being then taken by the alkyl residue. In this way one molecule of primary amine and one molecule of hydrogen halide are produced which combine to form the amine salt. As an illustration the interaction of methyl iodide and ammonia is given.



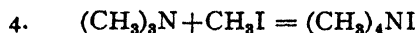
The alkyl halide next reacts with the primary amine, with the formation of a secondary amine,



which in a similar manner gives rise to a tertiary amine.



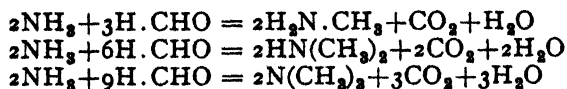
Finally the latter combines with more alkyl halide to form a quaternary ammonium salt.



The reaction velocities of the four reactions do not differ greatly and consequently a mixture of all four products is obtained. The ease with which the reaction occurs varies with the alkyl halide employed. Owing to greater convenience of manipulation, alkyl iodides are commonly used in the laboratory, whereas on the technical scale the cheaper alkyl bromides are preferred.

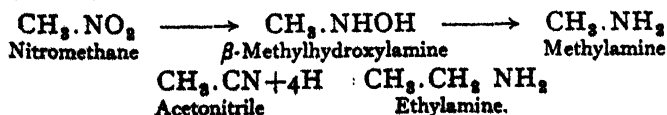
A convenient methylating agent, particularly for primary and secondary amines, has been found in *dimethyl sulphate*.

Another means of methylating primary and secondary amines is to heat them in acid solution with *formaldehyde*. This reaction can also be applied to ammonia and ammonium salts. The hydrogen atoms are thus successively replaced by methyl groups, three molecules of formaldehyde being required for the displacement of each two atoms of hydrogen.



The formaldehyde is generally introduced in the form of the 40 per cent. solution of commerce, and the reaction provides a simple and economical method of methylation capable of extensive application.

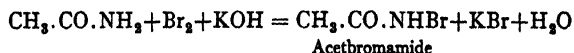
2. *Reduction Methods*.—Primary amines free from admixed secondary and tertiary derivatives are formed by the reduction of nitro- or nitroso-paraffins (p. 170) or of alkyl cyanides.



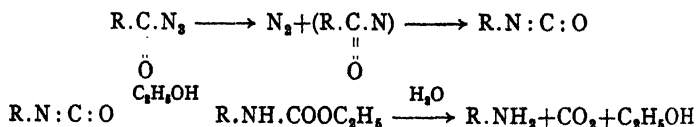
3. From carboxylic acids by the Hofmann, Curtius or Schmidt Reactions.



In the Hofmann method bromine and potassium hydroxide are brought into reaction with acid amides. The amine formed contains one carbon atom less than the amide employed, acetamide, for example, yielding methylamine, $CH_3.NH_2$. The reaction probably involves the conversion of acetbromamide by loss of HBr into methyl isocyanate, $CH_3.NCO$ (rearrangement). The latter then undergoes the normal decomposition with alkali to form amine and carbon dioxide.

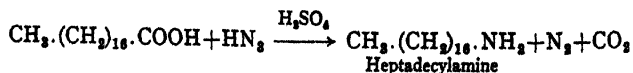


Acid azides are converted into amines by the Curtius degradation, which also involves a molecular rearrangement. The azides decompose quietly when warmed in alcohol solution, nitrogen being evolved and an isocyanate formed which reacts with the alcohol to give a urethane. With alkali the urethane is hydrolysed to alcohol, amine, and carbon dioxide.



Some acids are sensitive to bromine and cannot therefore be subjected to the Hofmann treatment. In such cases the Curtius method can be applied without difficulty.

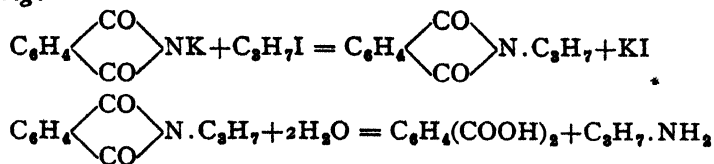
Schmidt¹ found that hydrazoic acid, generated from a cold saturated solution of sodium azide by 50 per cent. sulphuric acid and then extracted with benzene reacted with carboxylic acids to give amines, frequently in excellent yields.² For example, stearic acid gives heptadecylamine in 96 per cent. yield.



4. By *Gabriel's method*, using potassium phthalimide (see p. 536) This aromatic compound reacts with an alkyl halide to form an N-alkyl phthalimide, which on hydrolysis with hot concentrated hydrochloric acid breaks down into phthalic acid and a primary amine. The simultaneous formation of primary, secondary and tertiary amines occurring with free ammonia is here avoided by using as starting material an acid

¹ Schmidt, *Ber.*, 1924, 57, 704; 1925, 58, 2413. See also Oesterlin, *Angew. Chem.*, 1934, 536. ² Briggs, De Ath, and Ellis, *J.*, 1942, 61.

imide, $C_6H_4(CO)_2NH$, containing only *one* hydrogen atom attached to nitrogen, *e.g.*

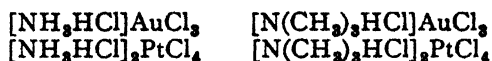


5. The simpler aliphatic amines are obtained commercially by the interaction of methyl or ethyl alcohol with ammonia in presence of a catalyst and separation of the resulting primary, secondary, and tertiary amines.

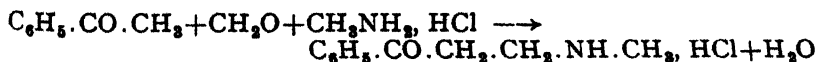
Properties and Chemical Behaviour.—As has been mentioned above, the amines strongly resemble ammonia in their power of forming salts and in many other properties. The lowest members are gases, readily soluble in water and possessing an ammoniacal odour. Unlike ammonia they are highly inflammable. The higher amines are liquids which also

	b.p. °C.
Methylamine	CH_3NH_2 -6.8
Dimethylamine	$(CH_3)_2NH$ 6.9
Trimethylamine	$(CH_3)_3N$ 3.5
Ethylamine	$C_2H_5NH_2$ 16.6
Diethylamine	$(C_2H_5)_2NH$ 55.9
Triethylamine	$(C_2H_5)_3N$ 89.5

dissolve in water, although the solubility diminishes with increase in molecular weight. Like ammonia the amines form double salts with the chlorides of certain metals, chief among which are gold and platinum; the composition of these compounds corresponds in most cases to that of the analogous derivatives of ammonia, *e.g.*,



Primary and secondary amines in presence of formaldehyde and hydrochloric acid react with compounds containing reactive hydrogen atoms, the latter being replaced by aminomethyl or substituted aminomethyl groups. For example, acetophenone reacts to give an amino-ketone.

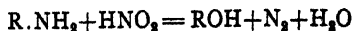


This reaction, known as the *Mannich Reaction*,¹ is of great synthetic value. Among the compounds which take part in the reaction are ketones, aldehydes, substituted acetic acids, picolines, etc.

Among the many reactions by which we may distinguish between primary, secondary and tertiary amines, the following may be noted.

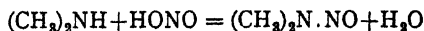
¹ An excellent account of the reaction is given by F. F. Blicke in *Organic Reactions* (Roger Adams), vol. 1, p. 303.

1. *Behaviour towards Nitrous Acid*.—Primary amines react with nitrous acid to yield primary alcohols, with evolution of nitrogen.



The reaction frequently is not so simple as this and is accompanied by isomeric change and olefin formation. Methylamine gives no methyl alcohol, but ethylamine gives 60 per cent. ethyl alcohol. *n*-Propylamine, on the other hand, gives 7 per cent. *n*-propyl and 32 per cent. *iso*-propyl alcohol along with 28 per cent. propylene.

Secondary amines yield nitrosamines.



Nitrosamines are yellow or yellow-red neutral oils of aromatic smell. From them the secondary bases may be regenerated by treatment with strong reducing agents or by boiling with concentrated hydrochloric acid. Nitrosamines are often of great value in the recognition and purification of secondary amines. When warmed with phenol and concentrated sulphuric acid, and then diluted with water and made alkaline with sodium hydroxide, they give an intense blue or violet coloration (*Liebermann's reaction*).¹ This colour reaction is characteristic of all nitrosamines and many other nitroso-derivatives (see p. 169).

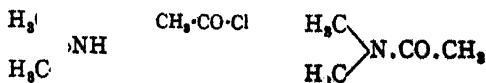
Tertiary aliphatic amines either fail to react with nitrous acid or undergo decomposition.

The above reaction may also be employed for separating secondary and tertiary amines from mixtures containing the primary compound, but in this case the latter is always destroyed.

2. *Behaviour on Alkylation*.—As will be seen from the details given on p. 175, it is possible to distinguish between primary, secondary and tertiary amines by treating them with methyl iodide until the whole of the replaceable hydrogen has been displaced by methyl groups. By analysis of the base before and after treatment we may determine how many methyl groups have entered the molecule, and thus classify the original amine.

This reaction is frequently employed in investigating the constitution of alkaloids.

3. *Behaviour towards acid chlorides*, such as benzene sulphonyl chloride. Primary and secondary amines interact with acid chlorides and anhydrides, an acyl group (*e.g.* CH_3CO) being substituted for the replaceable hydrogen of the base. Tertiary amines do not react.



¹ The colour is due to the formation of an indophenol (Decker and Solonina, *Ber.*, 1902, 3 3217), see. p. 516.

In general it is only possible to replace one of the two typical hydrogen atoms in a primary amine by means of acetylating agents, although diacetylation may occur in certain cases.

The acetyl and benzoyl derivatives are usually solid compounds of definite melting-point and are much used for the identification of amines.

On the other hand, with the aid of benzene sulphonic chloride, primary, secondary and tertiary amines may be distinguished and isolated from one another. The separation depends on the fact that primary amines react with benzene sulphonic chloride to form derivatives of the type $C_6H_5SO_2.NHR$, which readily dissolve in aqueous alkali, the hydrogen atom attached to nitrogen being replaceable by metals. Secondary amines on the contrary yield compounds of the type $C_6H_5SO_2.NR_2$, which are insoluble in alkali. Tertiary amines do not react at all. In some cases this method requires modification (Hinsberg).

Other characteristic reactions are the conversion of primary amines into the isocyanides by means of chloroform and alcoholic potassium hydroxide (p. 137); the reaction of primary and secondary amines with Grignard reagents (p. 143); and the interaction of tertiary amines with alkyl halides to form quaternary ammonium salts (see below).

Methylamine, $CH_3.NH_2$, is prepared by Hofmann's method (p. 176) from acetamide, bromine and caustic soda. It is a colourless gas with a smell resembling that of ammonia.

Dimethylamine, $(CH_3)_2NH$, occurs in herring brine and is best obtained from nitroso-dimethyl-aniline by heating with caustic soda (p. 472).

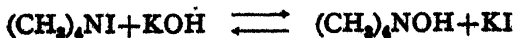
Trimethylamine, $(CH_3)_3N$, occurs in nature in many plants, and also in herring brine. On the large scale it is prepared by the distillation of beet molasses (see p. 243) or from herring brine. It is conveniently obtained in the pure state by heating ammonium chloride with formaldehyde.

Quaternary Ammonium Compounds

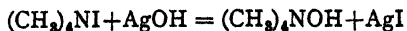
Tertiary amines combine characteristically with alkyl halides to form quaternary ammonium salts. Thus trimethylamine and methyl iodide yield tetramethylammonium iodide.



These quaternary salts resemble the amine salts in their physical properties, being crystalline, water-soluble substances. They differ, however, in their chemical behaviour. While amine salts and potassium or sodium hydroxide afford the free amines, the quaternary ammonium salts yield the corresponding quaternary ammonium hydroxides.



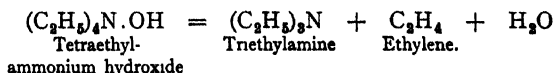
A quantitative yield cannot be obtained by this method unless it is carried out in methyl alcohol solution. The potassium halide then separates out and the reaction goes to completion. Another quantitative method is to use moist silver oxide.



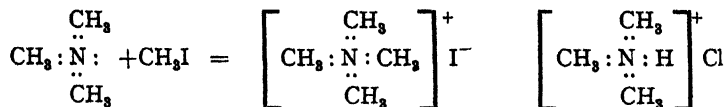
These hydroxides are very like caustic soda. They are colourless, hygroscopic solids, readily soluble in water to give strongly alkaline solutions. Strongly heated tetramethyl-ammonium hydroxide decomposes into trimethylamine and methyl alcohol.



The more complex ammonium bases break up under the influence of heat to give water, a tertiary amine and an olefin. This is the basis of the method of exhaustive methylation described later (p. 722).



Insight into the structure of the quaternary ammonium compounds is obtained by considering their electronic formulæ. In the formation of tetramethylammonium iodide the lone pair of electrons on the nitrogen atom of the base is used to bind the fourth methyl group. The iodine atom separates with both the electrons which bound it to the methyl group and consequently



is obtained as a negative ion. The nitrogen now has eight valency electrons, four of which may be considered as contributed by the carbon atoms and four by the nitrogen atom. Since nitrogen normally has five valency electrons this means that the nitrogen atom is the centre of a positive ion. In these quaternary compounds, therefore, the nitrogen atom is bound to the alkyl groups by four covalencies and the halide ion is linked to the rest of the molecule by an electrovalency.

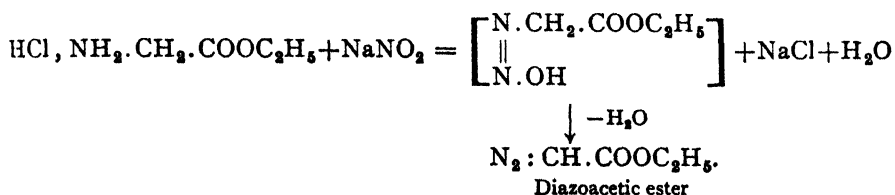
It is instructive to compare the above formula with those of the amine salts. Trimethylamine hydrochloride, for example, has the analogous structure (see above). Here again the main bonds are four covalencies and one electrovalency. The only difference from the quaternary ammonium compounds considered above is that the positive ion contains a hydrogen atom directly linked to the nitrogen. This hydrogen is readily removed as a proton by hydroxyl ions and hence these salts in the presence of bases such as sodium hydroxide yield the free amine. In the quaternary ammonium salts this hydrogen atom is lacking and they therefore yield with alkali the corresponding hydroxides.

Amine Oxides

Tertiary amines are smoothly oxidised by hydrogen peroxide to form amine oxides, R_3NO . Trimethylamine thus yields trimethylamine oxide. The formula, $R_3N = O$, previously assigned to these substances no longer finds acceptance (see p. 20) and there is good evidence that the oxygen is united to the nitrogen by a coordinate linkage; e.g. $R_3N \rightarrow O$.

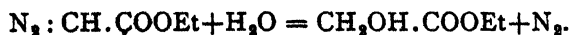
IV.—ALIPHATIC DIAZO-COMPOUNDS

Nitrous acid with simple aliphatic primary amines readily gives alcohols; with many compounds containing the primary amino group, however, the reaction is more complex. Outstanding examples are found in the primary aromatic amines (see p. 478) and the esters of α -amino acids, the latter giving not alcohols but aliphatic diazo-compounds. Glycine ester hydrochloride, for example, when treated with sodium nitrite yields a yellow liquid, *diazoacetic ester*.



Diazo-compounds of analogous constitution are also formed by the action of nitrous acid on the amines.¹ Only esters of α -amino-acids can be converted into diazo-esters; no diazo-compounds have been isolated from free amino-acids or from esters of β - or γ -amino-acids. In addition, it is necessary that one hydrogen atom should be united to the α -carbon atom. The most stable diazo-compounds are obtained from substances such as glycine ester, which contain the group $-\text{CH}_2\text{.NH}_2$ and as a result form derivatives in which a hydrogen atom still remains attached to the α -carbon atom.

The diazo-esters are very reactive. Diazoacetic ester, for example, in presence of dilute acids loses nitrogen to give the ester of glycollic acid.

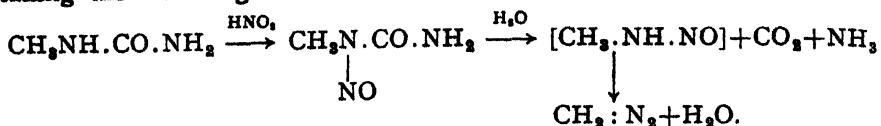


Diazoacetic ester is used in the preparation of *hydrazine*, $\text{NH}_2\text{.NH}_2$, and the conversion of the latter to *hydrazoic acid*, N_3H (Curtius); also in the synthesis of pyrazole derivatives (see index).

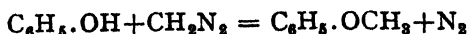
Diazomethane, the simplest aliphatic diazo-compound, N_2CH_2 , is a yellow, odourless and extremely poisonous gas. It is best prepared by

¹ Sidgwick, *The Organic Chemistry of Nitrogen* (Clarendon Press, 1937), p. 342.

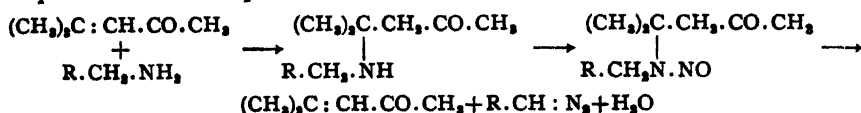
warming nitrosomethylurea with methyl alcoholic potash, the reaction taking the following course:—



Diazomethane is liable to explode like the other aliphatic diazo-hydrocarbons, but is more stable in solution. It readily decomposes with evolution of nitrogen and is a good methylating agent at room temperature, converting acids into their methyl esters and phenols into their methyl ethers. Enolic groups such as that in acetoacetic ester are also methylated, but alcohols, under ordinary conditions, do not react.



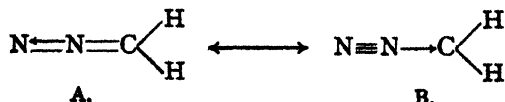
Higher diazo-hydrocarbons are prepared by Kenner's method¹ in which primary aliphatic amines are made to react with mesityl oxide. The resulting product with nitrous acid forms a N-nitroso compound, which is hydrolysed with sodium alkoxide to mesityl oxide and an aliphatic diazo-compound.



The diazo-group in the aliphatic diazo-compounds was formerly believed to have the cyclic structure such as that assigned to diazo-

methane $\begin{array}{c} \text{N} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{N} \end{array} \text{CH}_2$. This is not incompatible with the reactivity of these

compounds, but the evidence as a whole shows that the two nitrogen and the carbon atoms have a linear arrangement. Not only are three membered rings containing two nitrogen atoms seldom encountered, but physical measurements (particularly electron diffraction) favour the linear formula. It is now generally accepted that only two formulæ are admissible. Diazomethane, for instance, has the possible formulæ A and B.



These differ only in electronic distribution and should correspond to high values of dipole moment, although of opposite signs. The low dipole moment observed (1.4D) can be accounted for by assuming that diazomethane is a resonance hybrid of the two forms A and B. The real structure is thus intermediate between these extremes.

It should be noted that aliphatic diazo-compounds differ in their structure from the diazo-compounds of the aromatic series.

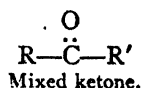
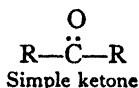
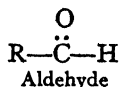
¹ E. C. S. Jones and J. Kenner, *J.*, 1933, 363; D. W. Adamson and J. Kenner, *J.*, 1935, 286

IX

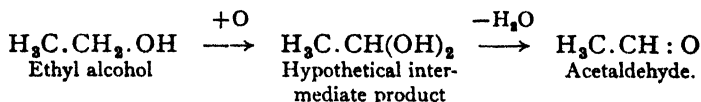
Aldehydes, Ketones and Ketenes

General Formulae and Nomenclature

Aldehydes and ketones are two important classes of compounds, both of which contain the carbonyl group $>\text{CO}$. In aldehydes the group is united on the one hand to a hydrocarbon radical and on the other to hydrogen; in ketones it is combined with two hydrocarbon radicals.

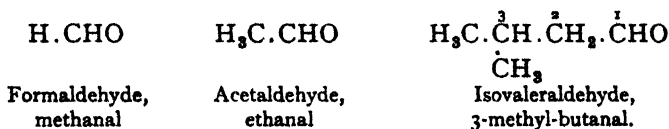


As already indicated on p. 147, **aldehydes** are the first oxidation products of primary alcohols (hence the name aldehyde, from *alcohol dehydrogenatum*). It may be assumed that the first step in this oxidation is the formation of a compound containing two hydroxyl groups attached to a carbon atom. Such derivatives, however, are unstable and generally lose water immediately to form aldehydes. For example:

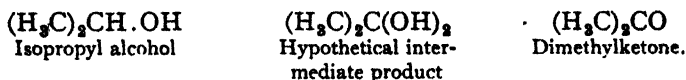


The aldehydes themselves readily undergo further oxidation to yield acids containing the same number of carbon atoms.

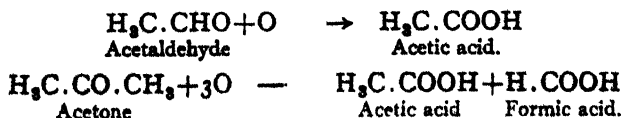
Individual aldehydes take their names from the acids produced from them on oxidation. According to the Geneva nomenclature, the name of an aldehyde is obtained from that of the parent hydrocarbon by the addition of the termination *-al*.



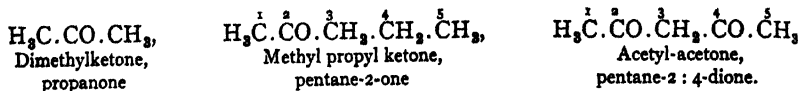
Ketones are oxidation products of secondary alcohols, and their formation may be represented in a similar manner to that of aldehydes.



They are far less readily oxidised than aldehydes, and as they contain no hydrogen atom attached to the carbonyl group it is not possible to obtain from them acids of the same number of carbon atoms. On oxidation they generally decompose with the formation of two acids of lower carbon content.

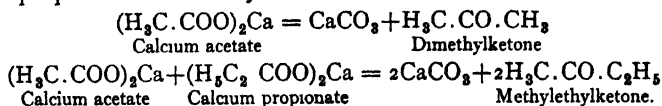


Ketones generally take their names from the alkyl groups present, but according to the Geneva nomenclature the names are derived from those of the parent hydrocarbons by the addition of the ending *-one*. Polyketones are distinguished as *-diones*, *-triones*, and so on.

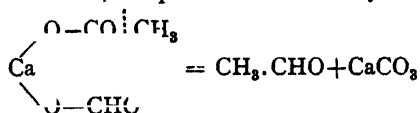


Preparation of Aldehydes and Ketones.—In addition to the oxidation of alcohols described above, the following reactions also lead to the formation of aldehydes and ketones.

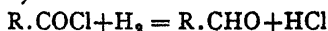
1. Dry distillation of the calcium, barium, thorium or lead¹ salts of carboxylic acids. In this way a ketone is produced containing two similar hydrocarbon radicals. By heating a mixture of the salts of two acids a certain proportion of the unsymmetrical ketone is obtained.



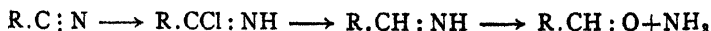
If, however, the salt of a fatty acid is heated with an equivalent amount of calcium formate, the product is an aldehyde.



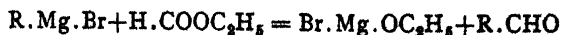
2. The above method, involving the use of formates, is limited to the preparation of those aldehydes which distil without decomposition. Since the carboxylic acids are usually readily accessible compounds, many attempts have been made to develop general methods for their conversion into aldehydes. One such method is the catalytic reduction of acid chlorides² (*Rosenmund*).



3. Some aldehydes may be prepared from the corresponding nitriles by shaking in the cold with a solution of anhydrous stannous chloride and hydrogen chloride in dry ether. The nitrile is stated to combine with HCl to form the imino-chloride, which is then reduced to the aldimine. On treating the mixture with aqueous acids, the aldimine is hydrolysed to aldehyde and ammonia.³



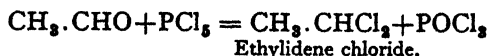
4. Aldehydes, together with secondary alcohols, may be prepared by allowing an excess of formic ester (3 mols.) to interact with organo-magnesium halides (1 mol.). The main reaction may be expressed by the equation



¹ J. Kenner and F. Morton, *Ber.*, 1939, 72B, 452. ² *Rosenmund, Ber.*, 1918, 51, 585
³ H. Stephen, *J.*, 1925, 1874.

5. Another useful method of preparing ketones is based on the decomposition of acetoacetic ester and its derivatives by alkalis (see acetoacetic ester).

Structure and Properties. The structures of the aldehydic and ketonic groups follow from the chemical behaviour of the parent compounds. Acetaldehyde, for example, with phosphorus pentachloride yields ethylidene chloride and phosphorus oxychloride.

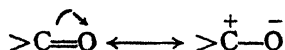


It follows that acetaldehyde contains the fragment $\text{CH}_3\cdot\text{CH}$; but no hydroxyl group since no hydrogen chloride is evolved in the reaction with phosphorus pentachloride. The only formula to satisfy these and

the normal valency requirements is $\text{CH}_3\cdot\overset{\text{O}}{\underset{\text{H}}{\text{C}}}$ Acetone likewise can

be shown to contain a carbonyl group between two methyl radicals. The formulæ given on p. 183 are therefore generally accepted and express satisfactorily the chemical properties of the compounds.

The carbonyl group which is common to both aldehydes and ketones can be written with a double bond between the carbon and oxygen atoms, but this form by electromeric displacement can give rise to the polar form with a positive charge on the



carbon atom and a negative charge on the oxygen. The first form should have only a small dipole moment, in contrast to that of the polar form which would be 5.95D. Since aldehydes and ketones have a moment of approximately 2.8 D it is clear that the carbonyl group is highly polar and is a resonance hybrid of the polar and non-polar forms. As will be seen later the polarity of the carbonyl group plays a decisive role in the chemical behaviour of the aldehydes and ketones.

The behaviour of both classes of compound on oxidation has already been described. The aldehydes are very easily oxidised and therefore possess reducing properties by means of which they may be detected. This is usually done by treating a moderately dilute solution of an aldehyde with an ammoniacal solution of silver nitrate when a more or less brilliant silver mirror is obtained. Aldehydes also reduced Fehling's solution with precipitation of red cuprous oxide.

Two other tests are also used to distinguish between aldehydes and ketones. A solution of rosaniline hydrochloride which has been decolorised by sulphur dioxide (*Schiff's reagent*) gives an intense reddish-violet colour with aldehydes. Aldehydes also react with an aqueous solution of the sodium salt of nitro-hydroxylaminic acid to give hydroxamic acids. On subsequent addition of ferric chloride a red colour is produced. This permits of the detection of very small quantities of an aldehyde.

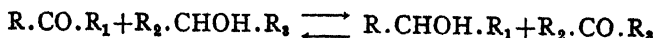
In all these tests ketones show a negative reaction.

The presence of a double bond in the carbonyl group is an indication of its unsaturation and leads to the expectation that aldehydes and ketones will form addition products such as are obtained from ethylene and other olefins. This, however, is true only to a limited extent. While the aldehydes and ketones are hydrogenated to the corresponding alcohols (see below), the characteristic feature of these compounds is their failure to form addition compounds with halogen or halogen hydrides and their reactivity towards reagents which normally do not add to ethylene. These reactions are discussed below.

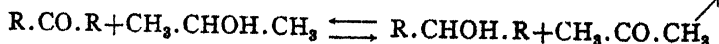
Reduction. Of importance in synthetic work is the reduction of aldehydes and ketones to the corresponding alcohols and hydrocarbons. On reduction with sodium amalgam, aldehydes are converted into primary alcohols and ketones into secondary alcohols.



This reduction, however, has serious disadvantages and frequently gives rise to pinacols (see p. 259). Two more reliable methods are now generally used. *Lithium aluminium hydride* is a very versatile reducing agent and reduces both aldehydes and ketones to give excellent yields of primary and secondary alcohols respectively under mild conditions.¹ In the second method, the *Meerwein-Ponndorf Reaction*,² the carbonyl compounds are reduced by means of alcohols. It has long been known that alcohols and



carbonyl compounds react only slowly even at high temperatures. Meerwein and Schmidt found, however, that in the presence of aluminium alkoxides aldehydes can be smoothly reduced by alcohols at 20-80°. Ponndorf enhanced the value of the method by also showing that ketones can be reduced by means of the aluminium derivatives of the more easily oxidisable secondary alcohols. In practice the aldehyde or ketone is heated with aluminium *isopropoxide* and *isopropanol*, and since the reaction is reversible the acetone as it is formed is continuously removed by distillation. The reaction is thereby carried to completion.

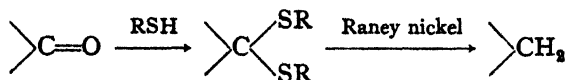


The Meerwein-Ponndorf reaction has many advantages over the older methods, particularly since it does not attack sensitive groupings such as ethylenic linkages, nitro groups, etc. On the other hand certain ketones such as acetoacetic ester, which enolise very readily, are not reduced owing to the formation of non-reducible aluminium enolates.

¹ R. F. Nystrom and W. G. Brown, *J.A.C.S.*, 1947, 69, 1199. ² A. L. Wilds, *Organic Reactions* (editor, R. Adams), vol. 2, p. 178. W. A. Johnson and G. E. H. Skrimshire, *Chem and Ind.*, 1951, 380.

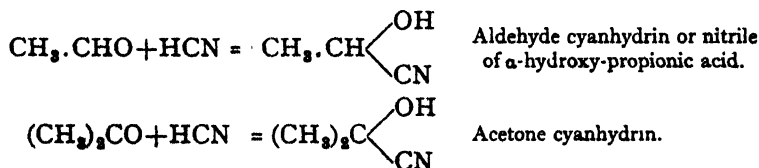
The reverse process whereby an alcohol is oxidised by a carbonyl compound was introduced by Oppenauer for the preparation of steroid ketones and it is in the steroid field that it has been most used. It is usually not possible to force this reaction to completion by removal of the alcohol formed since, in general, alcohols have higher boiling-points than the corresponding carbonyl compounds. The difficulty is partially overcome by using excess oxidising ketone. As a catalyst, aluminium *tert.*-butoxide is frequently used and the oxidants most commonly employed are acetone, methyl ethyl ketone, and *cyclohexanone*. The method has the advantage that double and triple bonds are not attacked.

The reduction of the carbonyl to the methylene group ($\text{CO} \rightarrow \text{CH}_2$), whereby aldehydes and ketones are converted to the corresponding hydrocarbons is effected by certain specific methods. Amalgamated zinc and hydrochloric acid (*Clemmensen method*), electrolytic reduction, and catalytic hydrogenation at high pressures are often used. A novel and effective reduction¹ is the formation of thioacetals by the action of mercaptans on the carbonyl compounds followed by reduction with Raney nickel.

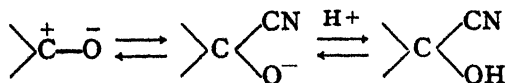


Another method frequently used is given on p. 189.

Addition Reactions.—Cyanohydrins. Both aldehydes and ketones combine with hydrogen cyanide to form cyanohydrins.



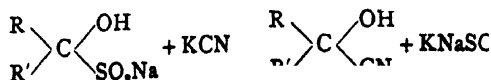
This reaction was shown by Lapworth to involve initially reaction of the carbonyl group with a cyanide *ion*, the reaction being completed by the instantaneous addition of a proton to the intermediate anion. There can be no doubt that the



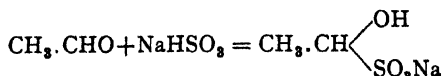
main reaction is attack of the polar carbonyl group by the nucleophilic (electron donating) cyanide ion. This exemplifies the fundamental difference between addition at the carbonyl group which, as we have just seen, is nucleophilic and addition to the ethylenic group which is electrophilic.

¹ M. L. Wolfram and J. V. Karabinos, *J.A.C.S.*, 1944, 66, 909.

The formation of cyanohydrins, in which a new carbon atom is added to the molecule, is of value in the synthesis of α -hydroxy-acids and α -amino-acids, as will be illustrated later. The cyanohydrins are also conveniently prepared from the bisulphite compounds (see below) by interaction with potassium cyanide.

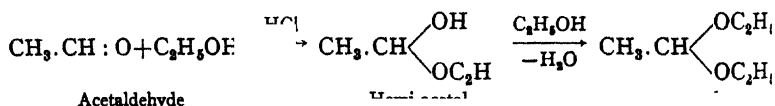


Bisulphite Compounds.—Aldehydes and methyl ketones unite with sodium or potassium bisulphite to give crystalline addition compounds, which are hydroxy sulphonates with a carbon-to-sulphur linkage.



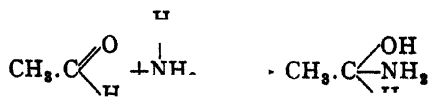
The bisulphite compounds are soluble in water from which they are easily "salted out", are insoluble in ether, and are used to separate aldehydes and ketones from other substances, since on warming with dilute acids or alkalis they yield the parent carbonyl compounds.

Acetals. Aldehydes in the presence of dry hydrogen chloride add on one molecule of alcohols to give *hemiacetals*. Further treatment with alcohols gives *acetals*. These



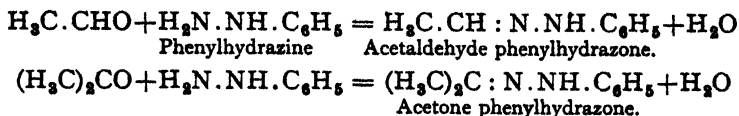
may be regarded as dialkyl ethers of the (sometimes unknown) hydrate. Acetals are relatively stable towards alkalis, but are readily hydrolysed by hot dilute acids. Ketones form acetals only under special conditions.

Reaction with Ammonia and its Derivatives.—When ammonia is passed into a cold ethereal solution of acetaldehyde a white crystalline precipitate of "*aldehyde ammonia*" is obtained. It is possible that an addition reaction first occurs:



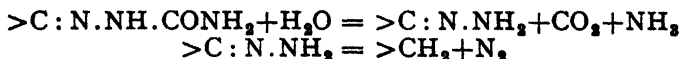
Further reaction, however, must occur as the molecular formula of aldehyde-ammonia at the ordinary temperature is three times the empirical formula. Other aldehydes such as formaldehyde and benzaldehyde react with ammonia in a different manner. Much more important are the reactions with derivatives of ammonia. Aldehydes and ketones react with derivatives of ammonia such as hydrazine, phenylhydrazine, hydroxylamine, and semicarbazide. Water is eliminated and products,

often crystalline, are readily obtained. With hydrazine, *hydrazones* are formed. *Phenylhydrazine* may be employed for this purpose,

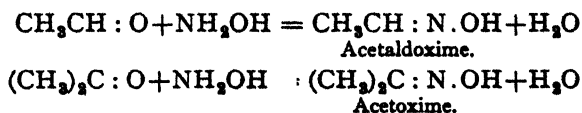


This reaction, which was first applied to acetaldehyde and benzaldehyde by E. Fischer, is of great service in the isolation and purification of aldehydes and ketones, since the phenylhydrazones usually crystallise well, and on heating with hydrochloric acid take up the elements of water to regenerate the original aldehyde or ketone. Phenylhydrazones are most readily formed in weak acetic acid solution. The higher melting 2 : 4-*dinitrophenylhydrazine*, $(\text{NO}_2)_2\text{C}_6\text{H}_3 \cdot \text{NH} \cdot \text{NH}_2$, is often employed in place of phenylhydrazine, since the resulting dinitrophenylhydrazones are beautifully crystalline compounds with suitable melting-points. *Semicarbazide*, $\text{NH}_2 \cdot \text{CO} \cdot \text{NH} \cdot \text{NH}_2$, has also proved of value for the isolation and identification of aldehydes and ketones, the *semicarbazones* obtained being in most cases more readily crystallisable than the corresponding phenylhydrazones.

Hydrazones and semicarbazones are converted into hydrocarbons on heating with sodium ethoxide (*Wolff-Kishner reaction*), the reaction taking the following course :



Hydroxylamine, NH_2OH , combines with aldehydes and ketones in the same manner as phenylhydrazine, water being split off and the residue : $\text{N} \cdot \text{OH}$ taking the place of the oxygen. The resulting compounds are termed *oximes* and are distinguished as aldoximes or ketoximes, according as they are derived from aldehydes or ketones.

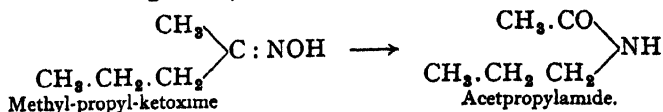


As in the case of the hydrazones, the oximes regenerate the original aldehyde or ketone on being heated with hydrochloric acid. Oximes possess basic as well as acidic properties, forming compounds of the type $\text{CH}_3 \cdot \text{CH} : \text{NOH}$, HCl and $\text{CH}_3 \cdot \text{CH} : \text{NOK}$. They usually crystallise well and are also used for the isolation and identification of aldehydes and ketones.

An interesting decomposition of aldoximes, to which reference is made later, is their tendency to break up under certain conditions so form water and a nitrile.

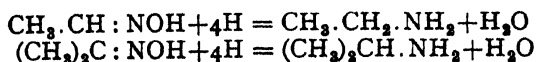
Under the influence of phosphorus pentachloride in ether or benzene (and of other reagents such as benzene-sulphonyl chloride, and solutions

of hydrochloric or sulphuric acid in glacial acetic acid),¹ the ketoximes undergo molecular rearrangement and are converted into acid amides (*Beckmann rearrangement*). For example,

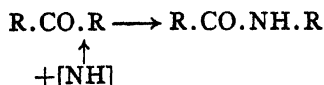


Under this treatment stereoisomeric ketoximes yield different products and the Beckmann reaction has therefore been employed as a general means of determining the structure of these compounds. (For further details see p. 53.)

On reduction both aldoximes and ketoximes are converted into primary amines.



Reaction with Hydrazoic Acid.—Aldehydes and ketones undergo the Schmidt reaction (p. 176) when treated with hydrazoic acid, N_3H , in the presence of a strong mineral acid or trichloroacetic acid. The ketones, for example, give substituted amides: *i.e.* the net result of the reaction is the insertion of an imino group (NH) into the molecule.



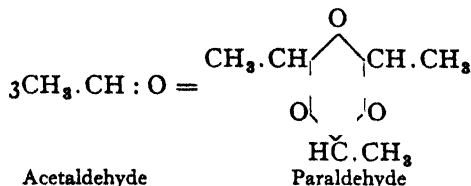
The method is of value not only for inserting a new carbon-to-nitrogen linkage in a molecule, but also for converting ketones into carboxylic acids, since the substituted amides are readily hydrolysed.

Reaction with Grignard Reagents.—Aldehydes and ketones combine with alkyl and aryl magnesium halides, as described on p. 150.

Condensation and Polymerisation of Aldehydes and Ketones.—Aldehydes have a strong tendency to undergo polymerisation and condensation. Both terms, especially the latter, are frequently misused and many reactions stated to be condensations are, strictly speaking, polymerisations; and vice versa. **Condensation** is a somewhat loosely defined term applied to those reactions involving the elimination of simple molecules such as water, alcohol, ammonia, etc. It generally involves the combination of two organic molecules, a new carbon-to-carbon linkage being established in the process. **Polymerisation** is the union of unsaturated compounds to form products (*polymers*) of the same composition but of different molecular weight (Berzelius, 1828). For example, when acetaldehyde, b.p. 22° , is mixed with concentrated sulphuric acid, polymerisation occurs with the evolution of much heat and the formation of a compound called *paraldehyde*, b.p. 124° , the molecular weight of which from vapour density determinations is found to be three times that of acetaldehyde.

¹ For a survey of these reactions see A. H. Blatt, *Chem. Reviews*, 1933, 13, 216. For the mechanism of the reaction see Brynmor Jones, *ibid.*, 1944, 24, 117.

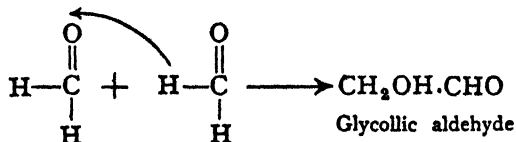
Paraldehyde no longer shows the typical aldehyde reactions, but is readily transformed into acetaldehyde by distillation with dilute sulphuric acid. From this it may be concluded that in the formation of paraldehyde three molecules of aldehyde combine together in such a manner that the carbon of one molecule unites with the oxygen of a second.



The ready depolymerisation of paraldehyde to acetaldehyde is noteworthy since ether linkages are generally not easily broken ; this does not apply, however, to many compounds containing the $-\text{C}-\text{O}-\text{C}-\text{O}-\text{C}-$ system.

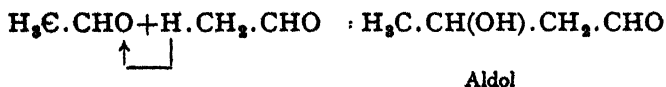
Aldehydes and ketones undergo condensations in the presence of suitable *condensing agents*. These condensations in the case of the aldehydes may be divided into two main types : (a) condensations in which α -hydroxyaldehydes are formed and (b) those in which β -hydroxyaldehydes are obtained.

(a) This type is illustrated by the condensation of formaldehyde by the action of alkali or calcium hydroxide. The process may be pictured as the transference of a hydrogen atom from one formaldehyde molecule to another.



Further reactions can occur and complex compounds such as sugars can be finally obtained (p. 194).

(b) In the second type of condensation homologues of formaldehyde take part, but though a migration of hydrogen occurs it comes from a neighbouring methylene group and not from the aldehydic group as in the first type of condensation. The classic example of this condensation is that of acetaldehyde, which under the influence of alkalis yields a compound containing an open chain of four carbon atoms which cannot be changed back into the original aldehyde by any simple method. In this case two molecules of aldehyde have combined with the simultaneous formation of a new carbon to carbon linking.



Combination of this type between aldehyde molecules is known as

the *aldol condensation*.¹ The same type of reaction may also take place between two different aldehydes, two ketones, or between an aldehyde and a ketone. The resulting aldehydic alcohols or ketonic alcohols readily split off water and pass into unsaturated aldehydes or ketones, *e.g.*



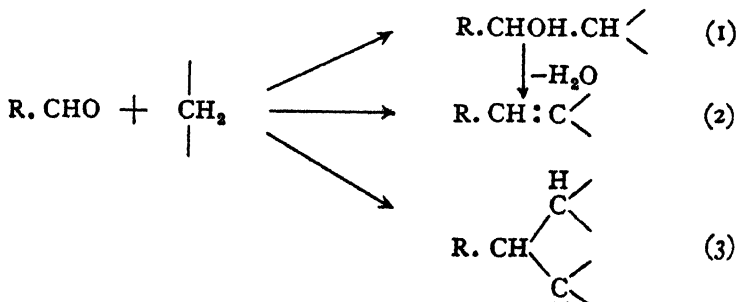
Crotonaldehyde

It may be pointed out that, although the term condensation is always applied to the formation of aldol from acetaldehyde, the process is really a polymerisation.

The condensation of aldehydes and, to a lesser extent, of ketones with compounds containing reactive methylene groups is of great synthetic and preparative value. Methylene groups in a hydrocarbon chain or ring do not enter into combination with aldehydes and ketones. They are, however, activated by the presence on contiguous carbon atoms of

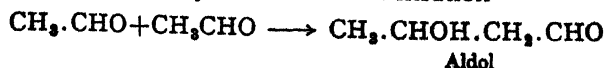
unsaturated groups such as carbonyl (>C=O), cyano ($\text{—C}\equiv\text{N}$), nitro ($\text{—N}\begin{smallmatrix} \text{O} \\ \diagup \text{ } \diagdown \\ \text{O} \end{smallmatrix}$), carboxyl ($\text{—C}\begin{smallmatrix} \text{O} \\ \diagup \text{ } \diagdown \\ \text{OH} \end{smallmatrix}$), and unsaturated ring systems.

Condensation with such compounds may occur in three ways as shown in the diagram.

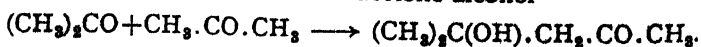


Examples of these different types of condensation are given below and throughout the book.

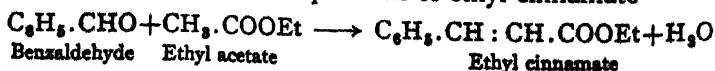
(1) Aldehyde and aldehyde. Aldol condensation



Ketone and ketone. Formation of diacetone alcohol



(2) Aldehyde and ester. Preparation of ethyl cinnamate

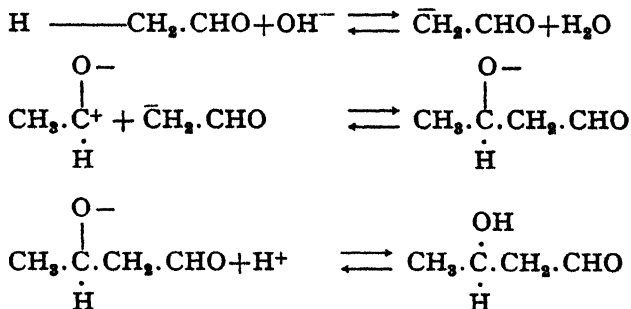


¹ The term aldol is derived from aldehyde-alcohol, the resulting compounds being both aldehydes and alcohols.

(3) Aldehyde and malonic ester. Preparation of ethyl propane tetracarboxylate



There is no doubt that the polar form of the aldehydes and ketones plays an essential role in the condensation reaction of these compounds, which are most frequently effected in the presence of basic catalysts. The presence of the electron-attracting carbonyl group in (say) acetaldehyde results in *incipient ionisation* of the compound so that with a base it readily loses a proton to give a carbanion. This then condenses with the other molecule of the aldehyde (in the polar form), and the reaction is completed by the addition of a proton to yield aldol.

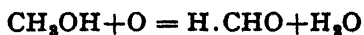


It can thus be understood why substances which contain the $\text{---CH}_2.\text{CO---}$ fragment are so often used in synthetic work.

Other examples of condensation and polymerisation are described in the sections dealing with formaldehyde and acetaldehyde.

SATURATED ALDEHYDES

Formaldehyde, methanal, $\text{H}.\text{CH}:\text{O}$, is formed by the oxidation of methyl alcohol, *e.g.* when the vapour of methyl alcohol mixed with air is led over heated catalysts such as silver, copper or platinum black.



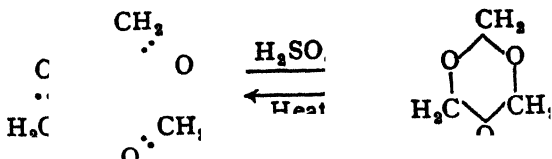
It is prepared on the industrial scale by passing a mixture of methyl alcohol and air over a heated copper catalyst. It is also manufactured in the U.S.A. by the controlled oxidation of methane under pressure. Methyl alcohol and acetaldehyde are obtained as by-products.

Pure formaldehyde is a gas at ordinary temperatures, but condenses under strong cooling to a colourless liquid of b.p. -21° . It possesses a pungent, penetrating smell, and is a powerful disinfectant. Formaldehyde is also employed for the preservation of anatomical specimens, since it possesses the property of transforming proteins into a hard, elastic

mass, insoluble in water. It is readily soluble in water and comes on to the market as a 40 per cent. solution, under the name of *formalin*. The latter usually contains from 12 to 18 per cent. of methyl alcohol, which is introduced during the process of manufacture and serves to prevent the formation of a sediment. Formaldehyde is a weakly acidic compound and yields salts with strong bases.

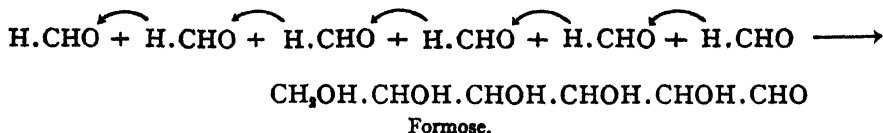
Polymerisation of Formaldehyde.—Formaldehyde polymerises in three ways.

1. When a 60 per cent. aqueous solution of formaldehyde containing a little sulphuric acid is boiled it polymerises to a crystalline trimer *trioxan* or *trioxymethylene*, from which formaldehyde may be

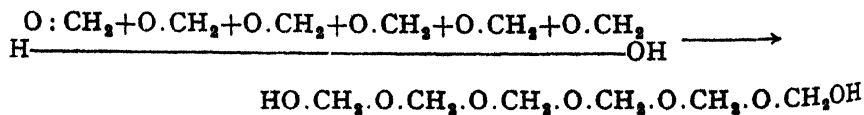


regenerated by heating. It is therefore a convenient substance for generating gaseous formaldehyde.

2. Butlerow (1861) obtained a sweetish syrup from a polymer of formaldehyde and lime, and Loew (1886) converted formaldehyde into a mixture of sugars—*formose*—with bases as condensing agents. The process is similar to that known as the aldol condensation (p. 191).

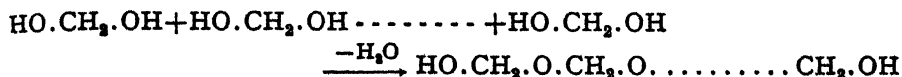


3. Long-chain polymers are obtained by the action of acids on aqueous or aqueous-methyl alcoholic solutions of formaldehyde. The products are known as *polyoxymethylenes* and their properties depend on the length of the chain. Moderate polymerisation yields a mixture of water-soluble polymers, while polymers containing more than a 100 formaldehyde molecules are amorphous and insoluble in water. They result probably by the following process:—



Strictly speaking, the above process is not polymerisation since the product is not a simple multiple expressed by $(\text{H} \cdot \text{CHO})_n$ and is generally now termed **condensation polymerisation**. Condensation polymerisation is effected by condensing together substances containing two or more functional groups to give long chain molecules. In the example just

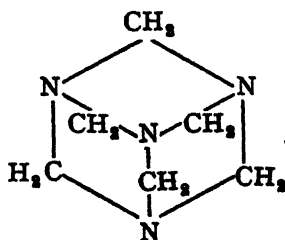
discussed the formaldehyde may be envisaged as reacting in the hydrated form, and many of the well-known polymers—



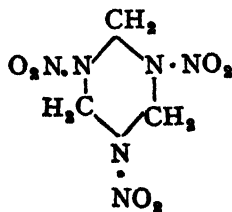
nylon, terylene, etc.—are condensation polymers.

Under the influence of strong alkalis, formaldehyde may either undergo the Cannizzaro reaction (p. 517) to give a mixture of formic acid and methyl alcohol, or a polymeride may be produced.

When treated with ammonia, formaldehyde does not yield an aldehyde ammonia, but gives a complex substance, *hexamethylene tetramine*, *hexamine* or *urotropine* $(\text{CH}_2)_6\text{N}_4$, m.p. 280° , which is employed medicinally as an internal disinfectant, especially for the urinary canal.



Hexamine



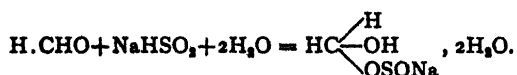
Cyclo-trimethylene-trinitramine.

The disinfectant properties possibly depend on the liberation of formaldehyde. The explosive, *cyclo-trimethylene-trinitramine*, is obtained by the nitration of hexamine.

Methylal, $\text{CH}_3(\text{OCH}_3)_2$, b.p. 42° , is frequently used in place of formaldehyde for condensations and is a very good solvent for many organic compounds. It may be prepared by cautious oxidation of methyl alcohol with manganese dioxide and sulphuric acid, or by the action of sodium methoxide on methylene iodide.

Formaldehyde condenses with phenols (p. 501) to form a hard resinous product (*bakelite*) which is utilised as an insulating material and for the manufacture of a variety of articles.

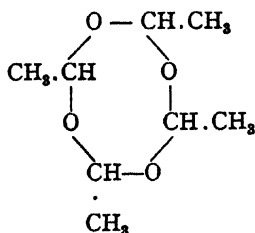
Formaldehyde-sodium sulfoxylate (*rongalite C*, *hydraldite*) is a reducing agent employed in vat dyeing. It may be prepared from formaldehyde and sodium hydrosulphite in alkaline solution.



Acetaldehyde, $\text{CH}_3 \cdot \text{CH} : \text{O}$, is formed by the methods indicated above, and is prepared both in the laboratory and on the large scale by the oxidation of ethyl alcohol with sodium bichromate and sulphuric acid. It is also obtained as a by-product in the manufacture of alcohol (see p. 155). The conversion of acetylene into acetaldehyde under the catalytic influence of mercury salts has been known for many years and

is used in its manufacture as well as that of acetic acid, $\text{CH}_3\text{CHO} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{CH}_2\text{OH}$. Acetaldehyde is a colourless, mobile liquid of peculiarly suffocating smell. It boils at $+21^\circ$, and is readily soluble in water, alcohol and ether. The presence of small amounts of acetaldehyde is best confirmed by condensation with dimethyl-cyclohexanedione (*dimedone*).

The most important polymerisations of acetaldehyde have already been described on pp. 190 and 191, but it may be added that it also polymerises under the influence of acids at temperatures below 0° to give *metaldehyde*. The latter forms long, glistening crystals which sublime at 115° without melting, being partially converted into ordinary aldehyde. It contains no carbonyl groups and has an eight-membered ring structure comparable to that of paraldehyde¹ (p. 191).



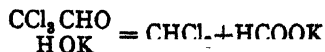
The following derivatives of acetaldehyde are of importance :—

Acetal, $\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2$, b.p. 104° , is formed together with aldehyde by the oxidation of alcohol. It is frequently used in place of aldehyde for condensation reactions.

Trichloro-acetaldehyde, chloral, CCl_3CHO , is a hypnotic which is obtained when chlorine is led into alcohol, first with cooling and finally at a higher temperature. It is assumed that the first step is the conversion of alcohol into aldehyde, chlorine acting as an oxidising agent, followed by substitution and the production of chloral, which is obtained united



with alcohol as the crystalline **chloral alcoholate**, $\text{CCl}_3\text{CHOH} \cdot \text{OC}_2\text{H}_5$. On distillation with concentrated sulphuric acid this yields chloral as an oily liquid, b.p. 97° , possessing a characteristic odour. On treatment with alkali at the ordinary temperature it decomposes into chloroform



and formic acid. This facile fission of a carbon-carbon linkage by alkali under mild conditions is remarkable and unusual.

Chloral hydrate, $\text{CCl}_3\text{CH}(\text{OH})_2$, is produced by the action of water on chloral; it forms readily soluble crystals, m.p. 57° , and is used as a

¹ L. Pauling and D. C. Carpenter. *J.A.C.S.*, 1926, 48, 1274.

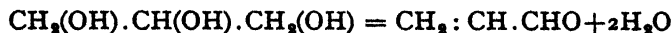
soporific. From the theoretical standpoint it is of interest as being one of the few compounds containing two OH groups bound to the same carbon atom.

n-Butyraldehyde, $C_4H_7 \cdot CHO$, is prepared commercially by oxidation of *n*-butyl alcohol and is used in the preparation of butyric acid and as a rubber accelerator.

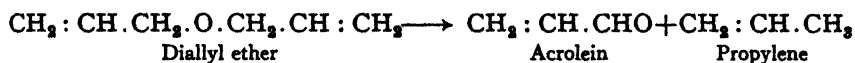
UNSATURATED ALDEHYDES

Unsaturated aldehydes show on the whole the same chemical reactivity as the saturated compounds, but owing to the presence of multiple bonds they also undergo those additive reactions characteristic of the unsaturated hydrocarbons.

Acrolein, acrylic aldehyde, $CH_2 : CH \cdot CHO$, can be prepared by removing the elements of water from glycerol by passing the vapour of glycerol over heated magnesium sulphate.



It is now prepared on the commercial scale by the pyrolysis or thermal cracking at $540^\circ C$. of diallyl ether, a by-product of the manufacture of allyl alcohol.



Some propionaldehyde is also formed by reduction of the acrolein.

It is a colourless liquid, b.p. 52° , which is difficultly soluble in water and has an extremely unpleasant pungent smell. The tendency of acrolein to polymerise is so great that it usually changes in a short time into a white, flocculent compound called *disacryl*. Acrolein is readily oxidised, even in the air, to form acrylic acid.

An unsaturated aldehyde of biochemical importance is **reductone**, $CH(OH) : C(OH) \cdot CHO$.

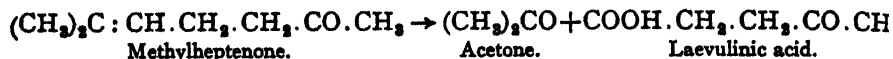
Crotonaldehyde, $CH_3 \cdot CH : CH \cdot CHO$, is produced by heating aldehyde with dil. hydrochloric acid, or with a solution of sodium acetate,



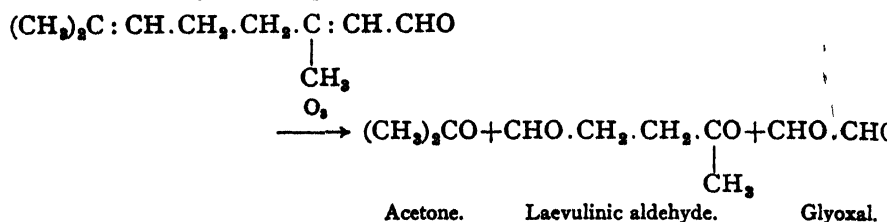
aldol being formed as an intermediate product. It is manufactured by heating aldol in nitrogen or carbon dioxide. It is a pungent-smelling liquid, b.p. 105° , which on oxidation is transformed into solid crotonic acid.

Citral, *geranial*, $(CH_3)_2C : CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3) : CH \cdot CHO$, is an important unsaturated aldehyde characterised by an intense aromatic lemon smell. It is much used by perfumers and flavourers. Lemon-grass oil contains about 70 per cent. of citral and provides the most convenient and cheapest source of preparation. On being heated with aqueous potassium carbonate, citral takes up a molecule of water and decomposes

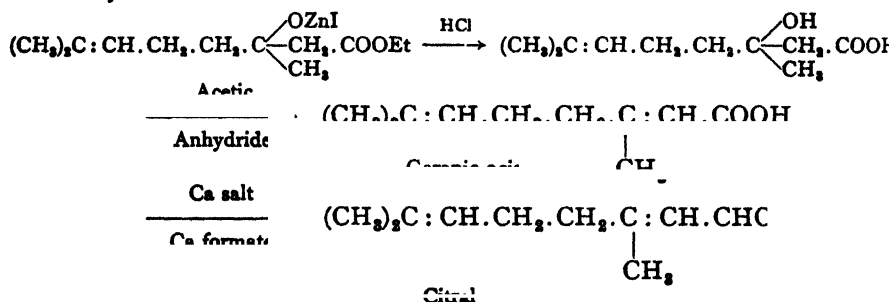
into methylheptenone and acetaldehyde. The constitution of the former follows from its oxidation to laevulinic acid and acetone.



These reactions give a clue to the structure of citral. The position of the double bonds is shown by the ozonisation of citral to give acetone, laevulinic aldehyde, and glyoxal.



The structure was confirmed by synthesis from methylheptenone and ethyl iodoacetate in the presence of zinc (*Reformatsky* reaction), the compound first formed yielding a β -hydroxy ester on treatment with dilute hydrochloric acid.



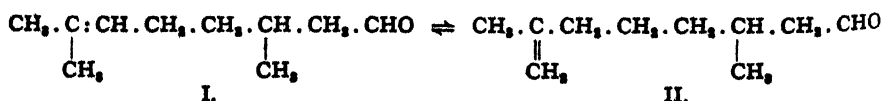
The citral of commerce is a mixture of two geometrical isomerides, α - (90 per cent.) and β -citral (10 per cent.), to which the following configurations have been assigned.



Natural citral on reduction yields the alcohol geraniol.

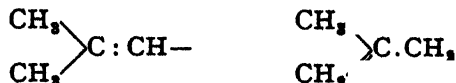
Citral is used in the manufacture of the perfumes, α - and β -ionones (see p. 200).

Citronellal is found in oil of citronella and eucalyptus. It is probably a tautomeric mixture of forms I and II.



It has a pleasant smell and is used in perfumery. On reduction it gives citronellol.

The problem as to whether the end groups in citral, citronellal, etc., are *isopropyl* or *isopropylidene* groups has aroused great controversy, see p. 394.



KETONES

Acetone, *dimethylketone*, *propanone*, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$, was formerly prepared industrially by the dry distillation of calcium acetate. Among the methods which have been more recently developed for production on the large scale the following may be mentioned :—

1. The Weizmann fermentation of corn, etc. (see p. 158).
2. The oxidation of isopropyl alcohol. This is the main industrial process.



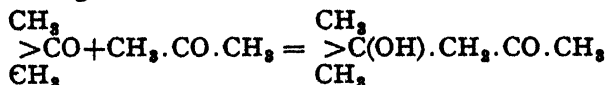
Acetone occurs in small quantities in blood and normal urine, and in larger quantities in the urine of diabetic patients. It is a liquid of pleasant smell which boils at 56° and is miscible with water, alcohol and ether in all proportions. The most important reactions of acetone have already been described on p. 185 *et seq.*, to which reference should be made. Acetoxime forms white prisms, m.p. 69° . Acetone, containing two methyl groups activated by a carbonyl group, participates in many condensation reactions. For example, with nitrous acid it yields *isonitroso-acetone*, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH} : \text{N} \cdot \text{OH}$ and *di-isonitroso-acetone*, $\text{HO} \cdot \text{N} : \text{CH} \cdot \text{CO} \cdot \text{CH} : \text{N} \cdot \text{OH}$. Another example of the reactivity of acetone is found in the synthesis of mesitylene (p. 450).

Acetone is an excellent solvent for a variety of organic compounds and forms the starting material in the production of chloroform, bromoform, iodoform and sulphonal.

The condensation of acetone leads to the formation of *unsaturated ketones*. These compounds combine the properties of ketones with those of ethylene.

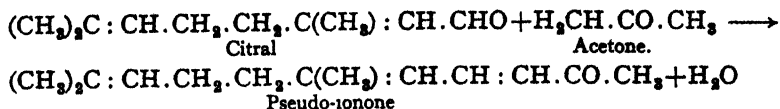
Mesityl oxide, $(\text{CH}_3)_2\text{C} : \text{CH} \cdot \text{CO} \cdot \text{CH}_3$, a colourless liquid, b.p. 122° , with a smell resembling peppermint and **phorone**, $(\text{CH}_3)_2\text{C} : \text{CH} \cdot \text{CO} \cdot \text{CH} : \text{C}(\text{CH}_3)_2$, m.p. 28° and b.p. 196° , are produced together by treating acetone with dehydrating agents such as hydrochloric acid, concentrated sulphuric acid or zinc chloride.

Another condensation product of acetone is *diacetone alcohol*, which is made by heating acetone with lime.

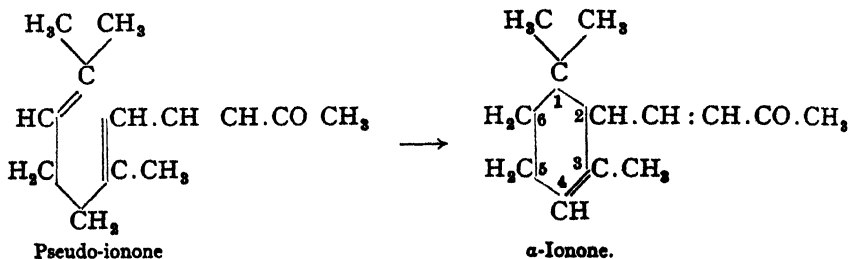


Homologues of acetone such as *methyl ethyl ketone*, *methyl isobutyl ketone*, *methyl n-amyl ketone*, etc., are now chemicals of industrial importance on account of their solvent properties.

Pseudo-ionone, $C_{15}H_{20}O$, is formed by the condensation of citral with acetone under the influence of baryta water,

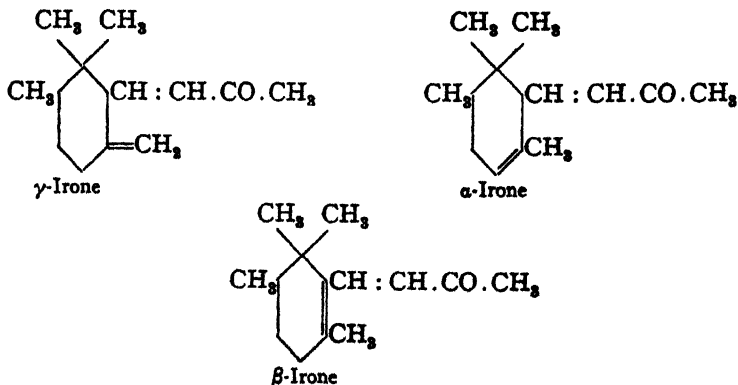


When boiled with dilute sulphuric acid it is readily transformed into a mixture of the isomeric ionones. The latter are reduced benzene derivatives which occur in two modifications as α - and β -ionones, having the double bonds in the ring in the Δ^3 and Δ^2 positions respectively.



Related to the ionones are the irones which occur in orrisroot and give rise to the pleasant perfume of the violet. As ionone strongly resembles irone in smell, it is prepared on a technical scale by the above method, citral or preferably lemon-grass oil being treated with acetone in the presence of an alkali (*e.g.* sodium ethoxide) and the pseudo-ionone so formed converted into ionone by means of sulphuric acid or sodium bisulphate.

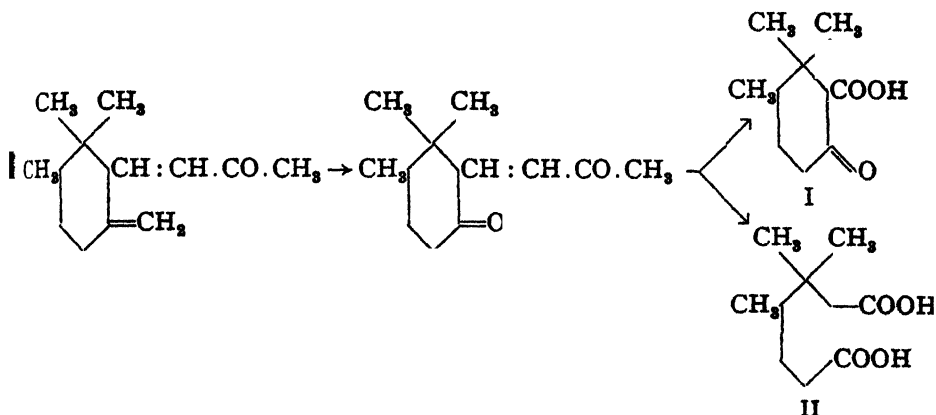
Irones.—The constitution of irone, first isolated by Tiemann and Rueger in 1893, has been the subject of considerable controversy. Ruzicka *et al.*¹ have now concluded that there are three irones, α -, β -, and γ -, of the following formulæ, all derived from 6-methyionone.



¹ L. Ruzicka, C. F. Seidel, H. Schinz and M. Pfeiffer, *Helv. Chim. Acta*, 1947, 30, 180; H. Schinz, L. Ruzicka, C. F. Seidel and C. Tavel, *ibid.*, 1947, 30, 1801. cf. Y. Naves, *ibid.* 1947, 30, 2221. See also S. H. Harper, *Ann. Reports*, 1947, 44, 146.

Natural irone is predominately a mixture of the α - and γ -forms both of which possess the "irone smell." Weak acids convert γ -irone into α -irone, and a third isomer, β -irone is obtained by treating either the α - or the γ -form with strong acid or alkali.

The structures assigned above have been confirmed by chemical and physical methods. The presence of the methylene side-chain is shown by the formation of formaldehyde on ozonisation, and the other products of the reaction, 2 : 2 : 3-trimethylpimelic acid (II) and the ketone I are formed as shown below.



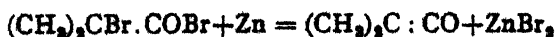
α -Irone and γ -irone have similar ultra-violet absorption spectra, with a band (λ_{max} , 230 m μ , ϵ_{max} , 4.2) corresponding to the α : β -unsaturated ketone fragment of the molecule, while the conjugated double bonds in the β -isomer are shown by absorption at a longer wave-length (λ_{max} , 300 m μ).

α -Irone has been synthesised.

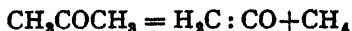
KETENES

The ketenes belong to a class of compound formally related to the ketones. They include *ketene*, $\text{CH}_2 : \text{CO}$, discovered by Wilsmore; substituted ketenes discovered by Staudinger, who also noted their extraordinary reactivity; and the double ketene of Diels, $\text{O} : \text{C} : \text{C} : \text{C} : \text{O}$, somewhat inaccurately called carbon suboxide. The characteristic group of the ketenes is $\text{>C} : \text{C} : \text{O}$. They are *inner anhydrides*, ketene itself being the inner anhydride of acetic acid.

Preparation.—The majority of ketenes of the general formula $\text{R}_2\text{C} : \text{C} : \text{O}$ have been prepared according to the method of Staudinger by acting on α -halogen-substituted acid chlorides with metals, preferably zinc, in hydroxyl-free solvents. In this manner dimethylketene is obtained from dimethyl-bromacetyl bromide.

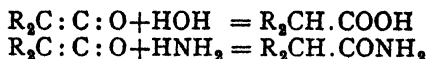


Ketene itself is readily prepared by the thermal decomposition of acetone, when ketene and methane are formed.

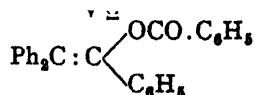
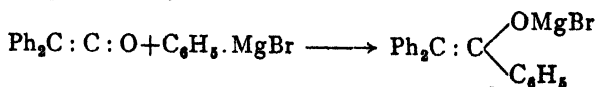


Ketene is made industrially by this method.

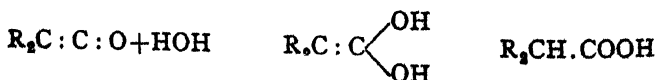
Properties and Reactions.—The ketenes, $\text{R}_2\text{C} : \text{C} : \text{O}$, belong to the large class of compounds containing two adjacent double bonds in the molecule, and are thus to be grouped with carbon dioxide, $\text{O} : \text{C} : \text{O}$, isocyanates, $\text{RN} : \text{C} : \text{O}$, and mustard oils, $\text{RN} : \text{C} : \text{S}$. With these they possess a number of reactions in common, although differing in their yellow colour. For example, ketenes react with water, alcohols, ammonia, amines and phenylhydrazine with the formation of acids or their derivatives.



Such reactions point to the extremely reactive nature of the ethylene bond and the inertness of the carbonyl group. While it is true that many reagents add on at the $\text{C}-\text{C}$ double bond and that the usual carbonyl reagents—phenylhydrazine, semicarbazide, etc.—fail to give characteristic derivatives with the carbonyl group, it has been shown that the latter reacts normally with Grignard reagents, etc. For example, phenyl magnesium bromide was shown to add on to the carbonyl group of diphenylketene, since the product on benzoylation proved to be the benzoate of triphenyl-vinyl alcohol.¹



Had addition occurred at the ethylene linkage, the product would be diphenyldibenzoylmethane. It may be concluded that the great reactivity of the ketenes is due to their system of double bonds, and that each double bond reacts with appropriate compounds. It may well be that with some reagents such as water addition occurs at the carbonyl group and is followed by isomerisation.



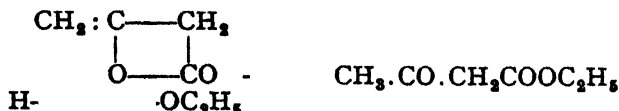
The ketenes show a strong tendency to polymerise, diketenes being formed. The structure of these dimeric compounds is still a matter of

¹ Gilman and Heckert, *J.A.C.S.*, 1920, 42, 1010.

controversy, but the probable formula for *diketene*—the most thoroughly studied compound of this type—is $\text{CH}_2 : \text{C} = \text{CH}_2$. Confirmation of this



structure is provided by ozonisation which yields formaldehyde and malonic acid.¹ Diketene is prepared commercially and is used in the manufacture of acetoacetic ester, etc.



It has great synthetic potentialities.²

Ketenes have been postulated as intermediates in many reactions.³ For example, the Arndt-Eistert synthesis (p. 205) is believed to involve a Curtius rearrangement which results in a ketene being formed.



In some cases the ketene has been isolated.

Ketene, $\text{CH}_2 : \text{CO}$, is a highly toxic, colourless gas with an exceedingly unpleasant pungent smell, reminiscent of both chlorine and acetic anhydride. In the pure state ketene is very unstable and can only be preserved at a low temperature. It is a powerful acetylating reagent, and is used in the manufacture of acetic anhydride.



THIO-ALDEHYDES AND THIO-KETONES

These compounds are produced by the action of hydrogen sulphide on aldehydes and ketones. They are liquids with a repulsive smell, and readily change by polymerisation into almost odourless compounds known as tri-thio-aldehydes or tri-thio-ketones. On oxidation with potassium permanganate they yield sulphones.

Thio-acetaldehyde, ethan-thial, $\text{CH}_3 \text{CH} : \text{S}$, is a repulsively smelling oil, not known in the pure state, which on treatment with acids is readily converted into *tri-thio-aldehyde*, $(\text{CH}_3 \cdot \text{CHS})_3$. The latter occurs in two modifications melting at 101° and 125° respectively, both of which are odourless and may be oxidised to give the same *triethylidene trisulphone*, $\text{C}_6\text{H}_{12}(\text{SO}_2)_3$.

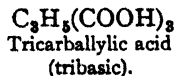
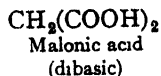
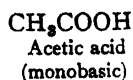
X

Monobasic Carboxylic Acids

The characteristic group contained in all these acids is the carboxyl group $-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ the hydrogen of which can be replaced by metals with the formation of salts. Consequently the basicity of the

¹ C. H. Hurd and C. A. Blanchard, *J.A.C.S.*, 1950, 72, 1461. ² For an interesting account of diketene see A. B. Boese, Jr., *Ind. Eng. Chem.*, 1940, 32, 16. ³ Wolff, *Ann.*, 1912, 394, 25; Eistert, *Ber.*, 1935, 68, 208; Lane, Willenz, Weissberger, and Wallis, *J. Org. Chem.*, 1940, 5, 276; Lane and Wallis, *ibid.*, 1941, 6, 443.

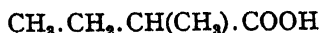
acids depends on the number of carboxyl groups present in the molecule. Those acids containing one such group are monobasic (monocarboxylic acids), and those possessing two such groups are dibasic (dicarboxylic acids), and so on, as illustrated by the following examples :—



The acids are called saturated or unsaturated according to the state of the hydrocarbon radicals attached to the carboxyl group. Monobasic saturated acids of the aliphatic series are commonly known as **fatty acids**, since many of them are prepared from fats.

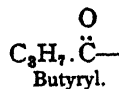
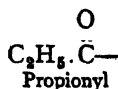
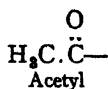
Nomenclature.—The names of the fatty acids all terminate in the syllable *-ic*, and generally indicate their source of preparation, as in formic acid (from ants), or the number of carbon atoms in the molecule, as in hexoic acid, $\text{C}_6\text{H}_{12}\text{O}_2$.

The English practice now is to employ either the common name in describing saturated monobasic acids and their derivatives, the positions of substituents being shown by the use of numbers or Greek letters, or another system in which the carboxyl group is regarded as a substituent and the α -carbon atom bears the number 1. The acid



can therefore be called α -methyl-butyric acid or 1-methyl-propane-1-carboxylic acid.

In the discussion of reactions it is frequently necessary to refer to that group of atoms which remains when the hydroxyl group is removed from a fatty acid; such groups, which are not capable of existence in the free state, are known as "acyl" groups or acid radicals, and are named after the corresponding acid by adding the termination *-yl* to a suitable contraction of the latter, *e.g.*



1.—SATURATED MONOBASIC FATTY ACIDS, $\text{C}_n\text{H}_{2n+1}\text{COOH}$

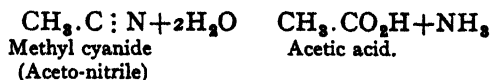
The fatty acids of low carbon content are corrosive liquids of pungent smell which distil without decomposition, dissolve readily in water and are acid in reaction. Those next in the series (C_4 to C_8) are oily compounds, sparingly soluble in water, and smelling unpleasantly of rancid butter or perspiration. The members from C_{10} upwards are solids, which are no longer soluble in water but dissolve readily in alcohol and ether; they cannot be distilled without decomposition except under diminished pressure.

Methods of Formation.—Of the numerous reactions available for this purpose only the most important are described here.

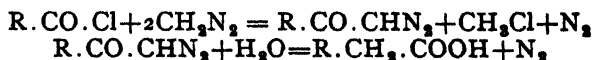
Saturated monobasic acids are produced :

1. By oxidation of the corresponding primary alcohol or aldehyde (p. 183).

2. By allowing alkyl iodides to react with potassium cyanide, and hydrolysing the alkyl cyanide or nitrile so formed.

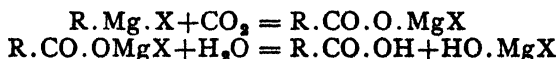


3. The *Arndt-Eistert method* is used to convert a carboxylic acid to its homologue.¹ The acid is converted into the acid chloride, which is then treated with diazomethane to yield a diazoketone. In presence of water and a catalyst (colloidal silver) the diazoketone decomposes to an acid.



The Arndt-Eistert reaction affords a method of increasing the number of carbon atoms in a chain.

4. Carboxylic acids may be readily synthesised by the method of Grignard, by treating alkylmagnesium halides in ethereal solution with carbon dioxide and decomposing the additive compound so formed with dilute sulphuric acid.



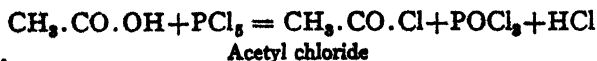
5. The hydrolysis of acetoacetic ester and its derivatives is a useful method for the preparation of monocarboxylic acids. This is described in detail later.

6. On the technical scale the higher fatty acids are prepared by the hydrolysis of fats.

Properties and Chemical Behaviour.—The carboxylic acids contain

the *carboxyl group*, $-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$, which gives a satisfactory expression of

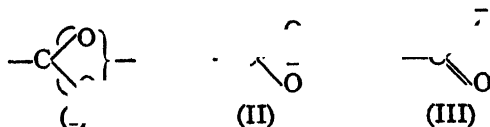
the chemical properties of the acids. The presence of the hydroxyl group is shown both by the ease with which its hydrogen atom (in contrast to other hydrogen atoms in the molecule) is replaced by metals and by its replacement by halogen when the acids are heated with phosphorus halides. Thus acetic acid and phosphorus pentachloride yield acetyl chloride.



The carboxylic acids, however, do not show the characteristic properties

¹ *Ber.*, 1935, 68, 200. For a general account of the reaction see W. E. Bachmann and W. S. Struve, *Organic Reactions*, 2, 38.

of the carbonyl group. This is attributed to the carboxylic ion exist in the mesomeric form I, which is symmetrically related to the two contributing structures II and III. The resonance energy is therefore high and the double bond



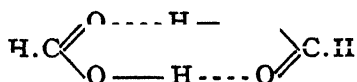
character of the carbon-oxygen link is greatly diminished. The same explanation serves for the unionised acid and for the esters and amides, although here the contributing structures are dissimilar and the mesomeric form will approximate more closely to one form.

The carboxylic acids give rise to a number of derivatives, acid chlorides, esters, amides, nitriles, etc. all of which on hydrolysis give back the acids. These derivatives are discussed in the next chapter.

With the exception of formic acid the majority of the fatty acids are little affected by ordinary oxidising or reducing agents. Hydrogen peroxide, however, reacts with them to yield per-acids, such as per-formic and peracetic-acid; and lithium aluminium hydride reduces them to primary alcohols.

As already noted (p. 176) the carboxyl group may be replaced by the amino-group.

Association of the carboxylic acids is often observed. Formic acid at high temperatures is monomeric and shows a characteristic infra-red absorption band at a frequency of 3570 cm^{-1} . This disappears at lower temperatures due to suppression of the hydroxyl characteristics by hydrogen bond formation.

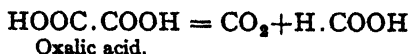


The removal of carbon dioxide from the carboxylic acids (decarboxylation) is generally carried out by heating them in the form of their sodium salts with soda-lime (see, e.g. p. 105).

Isomerism.—The number of structural isomerides theoretically possible for a carboxylic acid of given carbon content is the same as that for the corresponding aldehyde or primary alcohol, since the isomerism depends on the different arrangement of the carbon atoms in the hydrocarbon radical united to the carboxyl group. Among the first three members of the series, therefore, no isomerism is possible. The fourth, however, exists in two isomeric forms.

Formic acid, $\text{H} \cdot \text{COOH}$, occurs in ants, stinging nettles and many liquids of animal origin, such as perspiration and urine; it is obtainable from any of these sources by distillation with water. It may be formed according to the general methods given above, but is usually prepared by one of the following special methods.

Formic acid was originally obtained from oxalic acid by heating it with glycerol at 100° to 110° (Berthelot). Under these conditions the oxalic acid decomposes with the formation of certain intermediate products to yield chiefly carbon dioxide and formic acid.

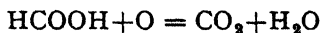


It is now manufactured by heating carbon monoxide with soda lime or sodium hydroxide under pressure. From the sodium formate thus produced, the pure anhydrous acid is prepared by distillation with sodium hydrogen sulphate.



Anhydrous formic acid melts at 8.6°, boils at 100.6°, and has a penetrating pungent odour. It is strongly corrosive and raises blisters on the skin. With water, alcohol and ether it is miscible in all proportions. The acid gives rise to salts known as *formates*, all of which dissolve in water, although those of lead and silver are only sparingly soluble.

Formic acid is oxidised by potassium permanganate with the formation of carbon dioxide and water, and in this respect differs from all its homologues.



Consequently it is a reducing agent, as is shown by its behaviour with silver and mercury salts. When heated with formic acid in aqueous solution the former yield a silver mirror and the latter mercurous salts.

Above 160° formic acid decomposes into carbon dioxide and hydrogen. The same reaction takes place at ordinary temperature under the catalytic influence of finely divided rhodium, iridium, or ruthenium, and less readily with spongy platinum. From this it may be concluded that the molecule has a tendency to split off molecular hydrogen according to the equation $\text{H.COOH} = \text{CO}_2 + \text{H}_2$. The reduction of formic acid by the addition of hydrogen would therefore be expected to present special difficulty and in fact, even under the most diverse experimental conditions, it is only possible to obtain minute yields of formaldehyde or methyl alcohol by the reduction of formic acid or its salts with hydrogen.

When formic acid is warmed with concentrated sulphuric acid it decomposes smoothly into pure carbon monoxide and water.



Acetic Acid, *Acidum aceticum*, $\text{CH}_3.\text{COOH}$

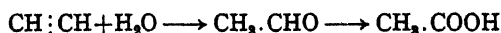
Salts of acetic acid are found in the saps of many plants and also in perspiration. From the practical standpoint the acid is one of the most important of the organic acids. It is prepared technically by the oxidation of dilute ethyl alcohol (wine, beer, etc.), by the dry distillation of wood and more recently from acetylene.

I. In the preparation of dilute acetic acid or *vinegar* from liquids containing alcohol, the oxidation is brought about by the action of air under the influence of bacteria, chiefly *Bacterium aceti*. This acetic fermentation occurs during the souring of beer or wines and leads to the formation of white or wine vinegar. Fermented liquids containing a small proportion of alcohol are utilised in this preparation. A more modern method known as the *quick vinegar process* is conducted in the following manner.

Large wooden vats are filled with basket-work or beech shavings moistened with strong vinegar containing acetic bacteria. The basket-work serves on the one hand to present a large surface of liquid to the oxidising action of the air, and on the other provides a suitable medium for the growth of the bacteria. The tubs are fitted with a perforated cover and the alcoholic liquid is run in and allowed to trickle slowly over the shavings. Air enters through holes in the lower walls of the vessel and passes upward in the opposite direction to the flow of the liquid. Oxidation is completed by repeating the process several times, the temperature being maintained at 30° to 35°. The whole reaction lasts about fourteen days and yields a table vinegar with about 6 to 7 per cent. of acetic acid.

II. Stronger acetic acid was formerly prepared by the dry distillation of wood (see p. 153), but this method is now only little used.

III. Most acetic acid is now manufactured from acetylene, which under the influence of mercuric salts combines with water to form acetaldehyde, air-oxidation of which yields acetic acid.

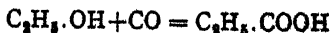


IV. A number of other industrial catalytic methods are being employed on an increasing scale. In one of these methanol and carbon monoxide combine at 300-400° C. in presence of a phosphoric acid catalyst to give a mixture of acetic acid and methyl acetate. Catalytic oxidation of ethanol or a mixture of propane and butane may also be mentioned.

Properties.—Anhydrous acetic acid melts at 16.6° to a corrosive liquid of pungent smell, which boils at 118°, and mixes with water in all proportions. The acid is hygroscopic, and stable towards oxidising agents such as chromic acid and potassium permanganate. Since it is an excellent solvent for many organic compounds it is often employed as such in oxidation reactions. Pure acetic acid should not decolorise one drop of a solution of potassium permanganate.

Acetic acid gives rise to salts known as *acetates*, most of which are soluble in water. *Acetates of aluminium, chromium, iron and copper* are largely employed as mordants in dyeing and printing.

Propionic acid, $\text{CH}_3.\text{CH}_2.\text{COOH}$, is manufactured by heating carbon monoxide and ethyl alcohol at 150°-350° under pressure in presence of a catalyst such as an acid or boron trifluoride.



It is a liquid of b.p. 141°, which resembles acetic acid.

Butyric Acids, $C_4H_7.COOH$

Two structural isomerides of this acid are possible :

1. **Normal butyric acid, fermentation butyric acid, $CH_3.CH_2.CH_2.COOH$,** occurs as the glyceryl ester (*butyrin*) in butter, and in the free state in perspiration. It is formed by the general methods available for the preparation of fatty acids, and is obtained on the large scale by the oxidation of butyraldehyde. It is known as fermentation butyric acid owing to its production under certain conditions during the fermentation of sugar, starch or lactic acid. It is a viscous, unpleasant smelling liquid, b.p. 163° .

2. **Isobutyric acid, dimethyl-acetic acid, $(CH_3)_2CH.COOH$,** boils at 154° . It resembles butyric acid in its properties, but is more easily oxidised.

Valeric Acids, $C_5H_9.COOH$

Four structural isomerides are possible, all of which are known, viz. :—

Normal valeric acid, $CH_3.CH_2.CH_2.CH_2.COOH$, b.p. 185° .

Isovaleric acid, $(CH_3)_2CH.CH_2.COOH$, b.p. 175° .

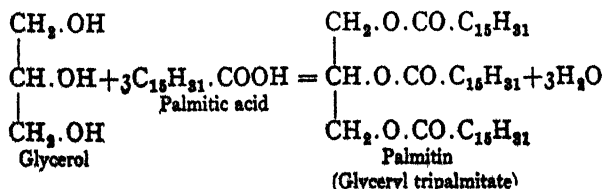
Methyl-ethyl-acetic acid, $(CH_3)(C_2H_5)CH.COOH$, b.p. 177° .

Trimethyl-acetic acid, $(CH_3)_3C.COOH$, b.p. 164° .

Isovaleric acid, ordinary valeric acid, $(CH_3)_2CH.CH_2.COOH$, occurs in the free state in many plants, particularly in valerian root, from which it is prepared by boiling with aqueous sodium carbonate. The product so obtained is the ordinary valeric acid, *Acidum valerianicum*, of pharmacy, and contains also some optically active methyl-ethyl-acetic acid. A similar mixture is obtained by the oxidation of fermentation amyl alcohol with chromic acid.

Higher Fatty Acids, Oils, Fats, Waxes and Soaps

Of the higher fatty acids, the normal members of the series with an even number of carbon atoms are found as esters in oils and fats of vegetable and animal origin. The most noteworthy of these are *palmitic acid*, $C_{16}H_{32}O_2$, melting at 62° , and *stearic acid*, $C_{18}H_{36}O_2$, melting at 69° . In frequent association with these two compounds are certain unsaturated acids, such as the liquid *oleic acid*, $C_{18}H_{34}O_2$. Oils and fats consist mainly of mixtures of the neutral glyceryl esters of these three acids, formed, as illustrated in the following equation, by the combination of the trihydric alcohol glycerol with three molecules of monobasic acid.



Waxes differ chemically from fats in being fatty acid esters, not of glycerol, but of higher monohydric alcohols of the methyl alcohol series such as cetyl alcohol, $C_{16}H_{33}OH$ (in *spermaceti*) and myricyl alcohol $C_{30}H_{61}OH$ (in *beeswax*). In addition, they also contain higher alcohol and acids in the uncombined state.

Of the glyceryl esters of the three acids named above, known as palmitin, stearin and olein respectively, the last has a considerably lower melting-point than the others

Palmitin	.	.	.	$C_8H_8(O \text{ CO } C_{15}H_{31})_3$	m p. 63°	}
Stearin	.	.	.	$C_8H_8(O \text{ CO } C_{17}H_{35})_3$	„ 65.5°	
Olein	.	.	.	$C_8H_8(O \text{ CO } C_{17}H_{33})_3$	„ -6°	

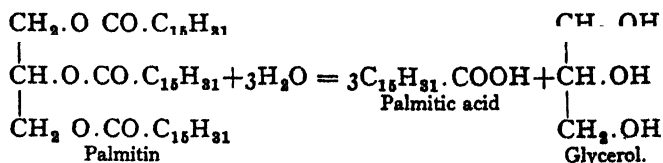
It follows, therefore, that the melting-point of a fat or oil, and its consistency at the ordinary temperature, depend very largely on the relative proportions of the glycerides present.

These oils and fats are obtained only from animal and vegetable sources. In plants they function like starch as food reserves, and for this purpose they are accumulated in the seeds and tubers. Animals also use vegetable oils and fats as food, employing them to build up new fats, which are deposited in the body and if required are available as reserves in time of hunger.

Oils and fats are prepared from naturally occurring products by expressing, melting or boiling out, or by extraction with solvents. Those intended for table use are generally expressed or melted out. When intended for other purposes all four processes may come into operation. Frequently the melting-out process is performed under pressure.

Fats are insoluble in water, and only sparingly soluble in alcohol; they dissolve readily in ether, carbon disulphide, benzene, chloroform and similar solvents.

On heating with alkalis (lime, magnesia, etc.), mineral acids, or with water at high temperature and pressure, fats are hydrolysed to form glycerol and fatty acids :—



This hydrolysis is brought about by the use of alkalis in the manufacture of soaps, which are alkali salts of the fatty acids. Hence the above reaction is sometimes termed *saponification*.

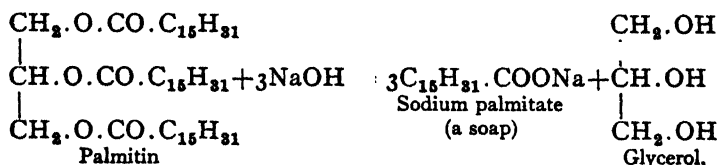
Hydrolysis may also be effected at relatively low temperatures (below 40°) by the action of the fat-hydrolysing enzyme *lipase* on an aqueous emulsion of the fat. Ferments of this type are present in the digestive organs and also in plants.

The free fatty acids required for the production of candles and glycerol, which is utilised nowadays for a great many purposes, are usually

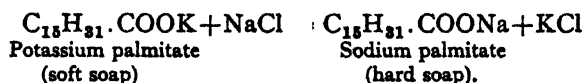
prepared by hydrolysing fats with sulphuric acid, or with water alone under high pressure (15 to 16 atmospheres) and temperature (*ca.* 200°). The raw materials most frequently employed are tallow, lard, coco-nut oil and palm oil.

As obtained by this process the mixture of fatty acids forms a semi-solid mass at ordinary temperatures, since it contains liquid oleic acid in addition to solid palmitic and stearic acids. Oleic acid is removed under pressure and used for the manufacture of soap. After admixture with a little wax to prevent crystallisation the solid acids are used in the production of "stearine" candles.

It has been stated that **soaps** are salts of fatty acids, and chiefly the alkali salts of palmitic, stearic and oleic acids. They are prepared by saponifying fats by boiling with caustic soda or potash. The reaction with palmitin, a fat very widely distributed in nature, is expressed by the equation :—



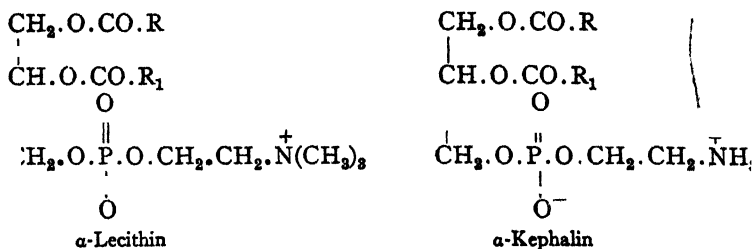
Hard soaps are sodium salts containing a preponderance of solid acids; *soft soaps*, on the other hand, are potassium salts with a high proportion of oleate. These soaps differ in solubility, and when potassium soaps are treated with excess of brine they are converted into the less soluble sodium soaps ("salting out" process).



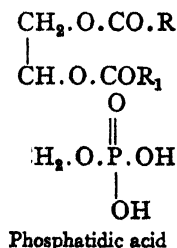
Sodium and potassium soaps dissolve in a small amount of water to give a clear solution, but in the presence of much water hydrolytic dissociation of the salt takes place with the formation of free acid and alkali. According to conditions, the free acid may remain suspended in the liquid in the form of oily drops or be precipitated in combination with the soap as a sparingly soluble acid salt. On the liberation of free alkali depends the cleansing action of soap. At this dilution the alkali loosens grease and dirt without attacking the skin or the material which is being cleaned. At the same time the precipitated salts envelop the particles of detached fat and dirt and prevent them from being again deposited on the fibres.

Synthetic detergents are now used for washing purposes. They are prepared by the hydrogenation of fatty acids (*e.g.* palmitic, stearic, oleic and lauric acids) at high temperature and pressure using a copper salt catalyst; the resulting alcohols, $\text{R}.\text{OH}$, are then converted into the sodium alkyl sulphates, $\text{R}.\text{O}.\text{SO}_3.\text{ONa}$. These salts lather well and are unaffected by hard water. Unlike ordinary soaps they are not hydrolysed in solution to give free alkali, hence they do not cause woollens to shrink.

Phospholipids. Closely related to the fats is a class of fat-like substances known as phospholipids (or *phosphatides*). They are essential components of all animal and vegetable cells and are found particularly in egg yolk, brain, heart, liver, and soya beans. They are triglycerides containing two long-chain fatty acids such as stearic or oleic acids and a phosphoric acid residue to which is attached a base. According to the nature of the base the phospholipids are termed *lecithins* or *kephalins*.



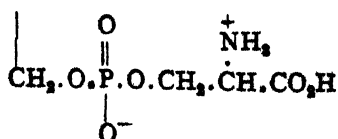
The lecithins contain the base choline (p. 263) and the kephalins contain β -aminoethanol (*cholamine*) (see, however, below). As will be seen from the formulæ they are derivatives of *phosphatidic acid*, salts of which have been obtained from beef heart.



The constitution of the phospholipids is deduced from their behaviour on hydrolysis with dilute alkali or acid. Glycerol, fatty acids, phosphoric acid, and a base are thus obtained.

The betaine formulæ assigned to the phospholipids are in harmony with their properties.

The lecithins are generally obtained for commercial purposes from soya beans. The kephalins are less soluble than the lecithins in ethanol and may be thus separated. It was at one time thought that all the kephalins were analogous to the lecithins except that the base present took the form of aminoethanol. It is now known, however, that besides these *phosphatidyl ethanolamines* there is another type of kephalin known as *phosphatidyl serines*, which as the name implies contain the amino-acid serine.



II.—UNSATURATED MONOBASIC ACIDS

1. Oleic Acid Series, $C_nH_{2n-1}COOH$

The best known member of the class is oleic acid, from which the series takes its name. These acids may be regarded as derivatives of the olefins C_nH_{2n} , and stand in the same relationship to the fatty acids as the olefins to the paraffins.

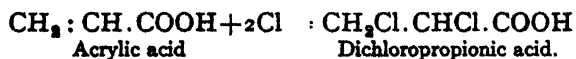
Unsaturated Fatty Acids

Acrylic acid . . .	$CH_2:CH.COOH$
Crotonic acid . . .	$CH_3.CH:CH.COOH$
Oleic acid . . .	$CH_3(CH_2)_7CH:CH(CH_2)_7COOH$
Sorbic acid . . .	$CH_3.CH:CH.CH:CH.COOH$
Geranic acid . . .	$(CH_3)_2C:CH(CH_2)_2C:CH.COOH$
	 CH_3
Linoleic acid . . .	$CH_3(CH_2)_4CH:CH.CH_2.CH:CH(CH_2)_7.COOH$

They may be obtained by methods analogous to those given for the fatty acids; also by the general methods available for the preparation of unsaturated compounds, *e.g.* by the removal of hydrogen halide from monohalogen substitution products of fatty acids (I), or of water from the corresponding monohydroxy acids (II).

I. $CH_2Cl.CH_2.COOH$	$CH_2:CH.COOH$
Chloro-propionic acid	Acrylic acid.
II. $CH_3.CHOH.CH_2.COOH$	$CH_3.CH:CH.COOH$
Hydroxy-butyric acid	Crotonic acid.

In chemical and physical properties these compounds strongly resemble the fatty acids, but they differ from them in certain points, particularly in their *addition reactions*. They combine with chlorine, bromine and iodine to form dihalogen derivatives, and with hydrogen halides to give monohalogen derivatives of the fatty acids. In the latter case halogen usually attaches itself to the carbon atom further away from the carboxyl group.

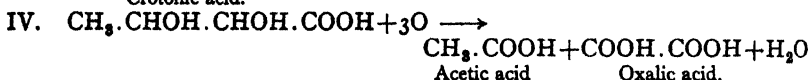
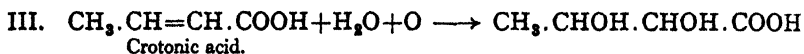


Unsaturated acids may be converted into saturated compounds by catalytic reduction. Thus when oleic acid is treated with hydrogen at ordinary temperatures in the presence of colloidal palladium it yields stearic acid. Mixtures of glycerides of saturated and unsaturated aliphatic acids, such as are present in animal and vegetable fats, may also be treated in the same manner. Castor oil, olive oil and cod-liver oil, which are rich in unsaturated glycerides, can be practically completely reduced by this process and thereby transformed into a crystalline, tallow-like mass of high melting-point. It is a matter of technical importance that other and cheaper catalysts, such as finely divided nickel (*Sabatier-Senderens*

process), may be used in place of palladium for this purpose, and also that pure hydrogen may be replaced by the gaseous mixtures of hydrogen obtained as industrial by-products. Under such treatment oils and soft fats generally yield a harder product which has many advantages, including a more pleasant taste and improved keeping qualities as compared with the starting material. For this reason the *technical hardening of fats* is of great practical importance in the manufacture of margarine.

Unsaturated acids unite with ozone to form unstable ozonides.

Another characteristic of unsaturated acids is the ease with which they undergo *oxidation* (*cf.* p. 124). With mild oxidising agents the first step is the addition of two hydroxyl groups to yield a dihydroxy acid (III). On further oxidation, disruption occurs at the point originally occupied by the double bond and two molecules of saturated acids are formed (IV). In this manner it is possible to ascertain the position of the double bond in an unsaturated acid.

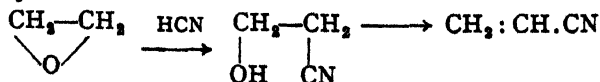


Isomerism among the acids of the oleic series may be of two kinds: (1) *structural isomerism* caused by a different arrangement of the carbon atoms in the hydrocarbon chain, or a different position of the double bond, and (2) *geometrical isomerism* (see p. 44).

Acrylic acid, $\text{CH}_2:\text{CH}.\text{COOH}$, is formed by oxidising acrolein with moist silver oxide, and is best prepared from ethylene-chlorohydrin as follows:



It melts at 7° , boils at 141° , and has a smell resembling that of acetic acid. It slowly polymerises on standing, and when reduced yields propionic acid. The nitrile, *acrylonitrile*, $\text{CH}_2:\text{CH}.\text{CN}$, is used in the manufacture of the synthetic rubber, Buna N. It is prepared commercially by the interaction of ethylene oxide and hydrocyanic acid, followed by dehydration of the product.



Crotonic acid is known in two stereoisomeric forms, namely

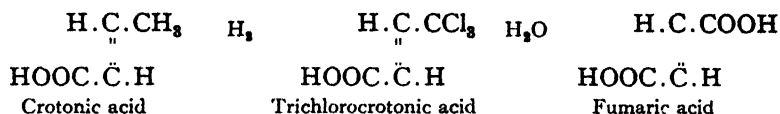


Crotonic acid (m.p. 72° , b.p. 180°) is best obtained by heating malonic acid with paraldehyde and acetic anhydride; isocrotonic acid by the

¹ J. H. N. van der Burg, *Rec. trav. chim.*, 1923, 42, 21.

distillation of β -hydroxyglutaric acid under reduced pressure. Isocrotonic acid is readily converted into the more stable crotonic acid by various means such as the combined action of sunlight and bromine in a solution of the acid in carbon disulphide or water. Many similar examples of stereoisomeric change are met with in organic chemistry.

The structures of both acids follow from reduction with zinc and sulphuric acid to *n*-butyric acid which proves they contain no branched chain and from the reactions given below. The *trans*-configuration of crotonic acid was neatly determined by von Auwers who showed that trichlorocrotonic acid gave on reduction crotonic acid and on hydrolysis fumaric acid. Since the conditions precluded isomeric change these results established clearly the relationship of crotonic to fumaric acid.



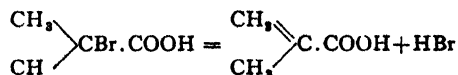
Isocrotonic acid therefore has the *cis*-configuration.

The above conclusions are in agreement with other properties of the acids.

Ozone reacts with an aqueous solution of isocrotonic acid, breaking up the molecule and forming acetaldehyde and glyoxalic acid. From this reaction the constitution of the acid may be deduced.



Methacrylic acid (m.p. 15° , b.p. 160.5°), occurs in oil of Roman camomile, *Anthemis nobilis*, and is formed from bromo-isobutyric acid by elimination of HBr:



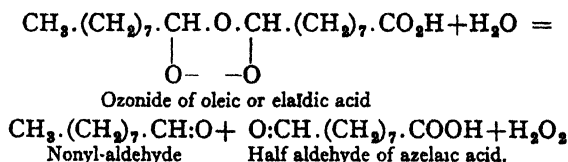
On reduction methacrylic acid yields isobutyric acid. It combines with bromine to give $\alpha\beta$ -dibromo-isobutyric acid, thus confirming the above constitutional formula. Methyl methacrylate is used in preparing synthetic plastics of great transparency (*perspex*).

Oleic acid, $\text{CH}_3 \cdot (\text{CH}_2)_7 \cdot \text{CH} : \text{CH} \cdot (\text{CH}_2)_7 \cdot \text{COOH}$, is found as the glyceryl ester, *triolein*, especially in the fatty oils (such as almond oil or olive oil), from which it is obtained as a by-product after hydrolysis in the manufacture of stearic acid (see p. 210). By taking advantage of the solubility of the lead salt in ether it may be separated from stearic and palmitic acids. At ordinary temperatures it is a colourless, almost odourless and tasteless liquid. At 4° it solidifies to a mass of colourless needles, which melt again when the temperature is raised to 14° . In contact with air, however, it rapidly becomes yellow owing to oxidation, and acquires a sour, rancid smell. Oleic acid gives stearic acid on reduction and dibromostearic acid on treatment with bromine, hence like stearic acid it contains a normal straight chain of carbon atoms. Further, the double

bond must be situated in the middle of the molecule, since careful oxidation leads to the formation of a mixture of *pelargonic acid*, $C_9H_{17} \cdot COOH$, and *azelaic acid*, $HOOC(CH_2)_7COOH$.

Nitrous acid converts oleic acid into a solid compound, **elaïdic acid**, m.p. 51° . This possesses the same structure as oleic acid, with which it is stereoisomeric. The relationship between oleic and elaïdic acids is thus similar to that existing between the two crotonic acids. Oleic acid is the *cis*- and elaïdic acid the *trans*-form.

Proof of the stereoisomerism of oleic and elaïdic acids is based on the observation that the dibromides of both these acids can be converted into the same *stearolic acid*, $C_{18}H_{33}O_2 \cdot C \equiv C(CH_2)_7COOH$. Additional confirmation is found in the manner in which the ozonides of the two acids are decomposed by water.

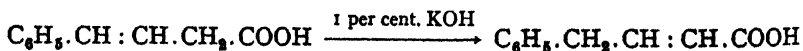


In the presence of air the half aldehyde of azelaic acid is rapidly oxidised to azelaic acid.

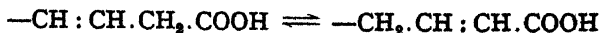
Oleic acid is used in the manufacture of soap.

Isomerisation of Unsaturated Acids

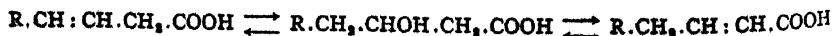
β : γ -Unsaturated acids tend like other β : γ -unsaturated systems to rearrange under the influence of alkalis, aliphatic amines, or piperidine to the (usually) more stable α : β -unsaturated acids. For example, 2-benzylidene-propionic acid with 1 per cent. potassium hydroxide gives 3-phenylcrotonic acid.



The reaction, however, is reversible and is an example of three-carbon tautomerism (p. 59).

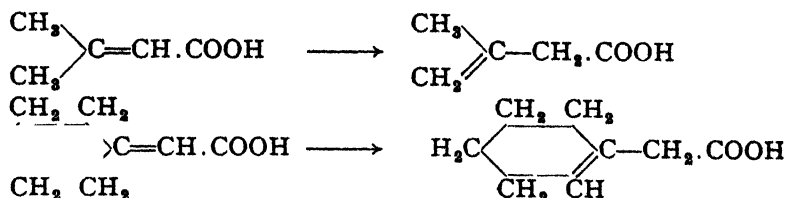


This reversibility is shown by the formation of some β : γ -acid by the action of alkali on an α : β -acid. The formation of an equilibrium mixture is explained by Fittig's postulate of the formation of an intermediate β -hydroxy acid which loses water according to the following equation :

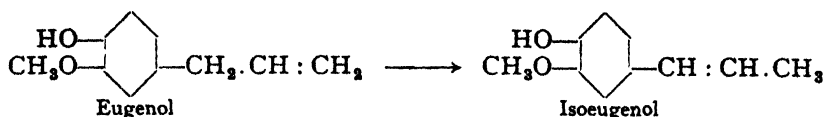


Among the acids investigated by Fittig the direction of the shift was from the $\beta\gamma$ - to the $\alpha\beta$ -position. Kon and his co-workers, who

examined a large number of cases of this nature, showed that the mobility of the hydrogen atom and the relative stability of the two forms depend on the nature of the other groups present in the molecule. For example, in the *gem*-dialkyl acrylic acids and cyclo-hexylidene-acetic acids, the $\beta\gamma$ -unsaturated derivatives are the more stable.



A similar isomeric change occurs in the transformation of eugenol into isoeugenol under the influence of hot alkalis, and in many terpene derivatives.



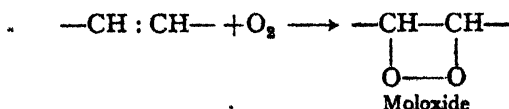
Autoxidation ¹

By autoxidation is meant the oxidation of certain substances by molecular oxygen. It is defined more precisely by Waters as oxidation by oxygen gas at normal temperatures without the intervention of a visible flame or of an electric spark. Very reactive intermediates are formed which can oxidise other molecules of the original substance or other substances which normally would not be oxidised. Indigo, for instance, is easily bleached in the presence of turpentine. Other characteristics of autoxidation are photochemical activation and susceptibility to positive and negative catalysis, characteristics which suggest the mechanism involves chain reactions.

Autoxidation is of enormous practical importance as exemplified by the autoxidation of rubber, drying oils, etc.

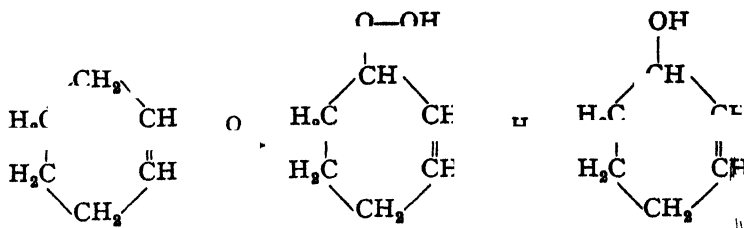
The autoxidation of olefinic substances such as linoleic, elaidic, or oleic acids has long been known and the formation of intermediate peroxides recognised. It is only recently, however, that the mechanism of the reaction has been elucidated. As an example, the autoxidation of olefinic compounds at moderate temperatures may be cited.

The formation of peroxides by the addition of oxygen molecules was plausibly explained by addition at the double bond to give a "moloxide" (*Engler-Bach* theory).



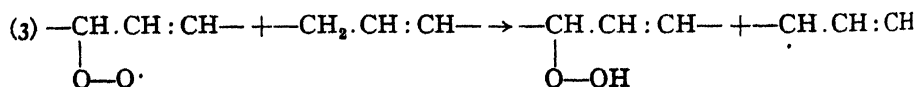
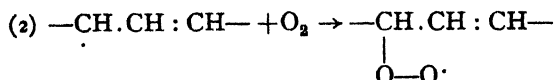
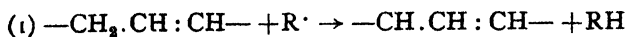
¹ W. A. Waters, *Ann. Reports*, 1945, 42, 131.

It is now known, however, that oxygen attacks not at the double bond, but at a methylene group adjacent to it with the formation of a *hydroperoxide*. R. Criegee, for instance, showed that cyclohexene and oxygen



give a hydroperoxide (see formula) since it can be reduced to cyclohexen-3-ol, contains one active hydrogen atom, and is unsaturated (absorbs one molecule of bromine). E. H. Farmer has shown as the result of analytical investigations that unconjugated olefins absorb oxygen to form quantitatively unsaturated hydroperoxides, $\text{R}-\text{O}-\text{O}-\text{H}$.

Now as Farmer pointed out this methylenic activity of olefins is unknown among their ionic reactions and is typical of the interaction of olefins and free radicals generated from dibenzoyl peroxide, etc. He therefore pictures autoxidation as a chain process involving free radicals and initiated by them.



This mechanism explains satisfactorily the known facts. It may be mentioned in passing that the methylenic attack involved is used to detect the presence of free radicals in chemical reactions (see, for example, the preparation of allyl chloride and 3-bromocrotonic acid).

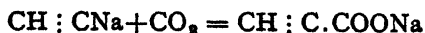
The subsequent decomposition of the hydroperoxides is dependent on factors such as acidity, etc., and is probably a complicated process. Alcohols, glycols, ketones, etc., are obtained.

2. Acids containing an Acetylene Bond. Propiolic Acid Series, $\text{C}_n\text{H}_{2n-3}\cdot\text{COOH}$

These acids may be considered to be derivatives of the acetylene hydrocarbons, and are formed from acids of the oleic series in the same manner as the acetylenes are formed from the olefins, *i.e.* by the addition of halogen and subsequent removal of 2 mols. of hydrogen halide.



They are also produced by the action of carbon dioxide on sodium derivatives of the acetylene hydrocarbons.



Like the acetylene hydrocarbons, these acids possess additive properties, and yield explosive compounds with ammoniacal solutions of silver and copper.

Propiolic acid, propargylic acid, $\text{CH} \equiv \text{C.COOH}$ (m.p. 9° , b.p. 144°), corresponds to propargyl alcohol.

XI

Derivatives of Monocarboxylic Acids

I.—DERIVATIVES FORMED BY SUBSTITUTION IN THE CARBOXYL GROUP

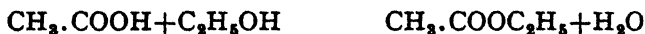
The substances discussed in this chapter are derivatives of the carboxylic acids in which the hydroxyl group is replaced by an atom or group of atoms.



They are all characterised by undergoing hydrolysis to the parent acids.

1. Esters

Methods of Formation.—In properties and methods of formation the esters of monocarboxylic acids resemble the esters of the mineral acids (see p. 162). Thus they may be prepared by the direct interaction of acid and alcohol, a reversible reaction which proceeds towards equilibrium.

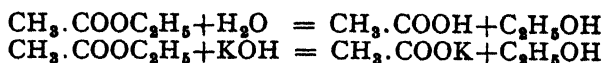


In the preparation of the ester by this method the backward hydrolytic action of the water is reduced to a minimum by the addition of concentrated sulphuric acid or dry gaseous hydrochloric acid. A common method of *esterification* is to boil the organic acid for several hours with excess of the alcohol, to which has been added 3 to 5 per cent. of hydrogen chloride or sulphuric acid (Fischer-Speier method). The ester is then isolated by pouring the mixture into water, in which the alcohol and acid usually dissolve without difficulty, leaving the ester as an insoluble oil.

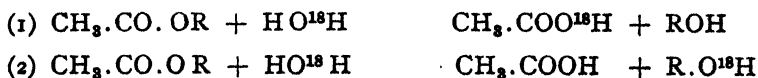
Insight into the mechanism of many organic and biochemical reactions has been obtained by the use of isotopes. Hydrogen may be replaced by deuterium and similar replacements have been effected by the use of the isotopes of nitrogen (N^{15}), oxygen (O^{18}), chlorine (radio-active chlorine), etc. In this way atoms and groups of atoms in molecules may be "labelled" or "tagged" and their fate in any given chemical

Properties.—The esters of lower molecular weight are colourless liquids with a pleasant fruity odour. Many of them are therefore prepared on a large scale in industry for use as artificial fruit essences. They are generally insoluble in water, but soluble in alcohol and ether. The boiling-point of an ester with a simple alkyl group (CH_3 , C_2H_5 , C_3H_7) is lower than that of the corresponding acid, but with the entrance of larger alkyl groups the position is reversed.

When esters are superheated with water, or boiled with alkalis or mineral acids, they undergo **hydrolysis** to regenerate the component acids and alcohols (see *saponification* and *hydrolysis*, p. 162).



The course of hydrolysis of the esters of carboxylic acids was also clearly demonstrated by the use of the heavy oxygen isotope. The alkaline hydrolysis of an ester might be supposed to proceed in either of the following ways :—



By making use of water containing O^{18} Polanyi and Szabo¹ found that the alkaline hydrolysis of amyl acetate takes place by the first process, since the amyl alcohol liberated contains the normal oxygen isotope O^{16} .

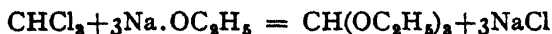
Owing to the ease with which the alkoxy group, —OR, can be replaced by other groups, esters are reactive compounds. Thus on treatment with ammonia they are converted into acid amides, and with phosphorus pentachloride into acid chlorides (see below).

When an ethyl ester is warmed with methyl alcohol and a catalyst (e.g. CH_3ONa or HCl) a reversible change occurs and the corresponding methyl ester is formed. Other esters and alcohols behave in the same manner. This is known as **alcoholysis**.

For reactions of esters with organo-magnesium halides see p. 144.

Ethyl formate, $\text{H}\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$, b.p. 55° , is used for flavouring artificial rum or arrak.

Ethyl orthoformate, $\text{CH}(\text{OC}_2\text{H}_5)_3$, b.p. 146° , is obtained when chloroform is heated with sodium ethoxide in alcoholic solution,



and is frequently used for synthetic purposes.

Ethyl acetate, $\text{CH}_3\cdot\text{CO}\cdot\text{OC}_2\text{H}_5$, b.p. 78° , is manufactured in large quantities from alcohol, sulphuric acid, and acetic acid or sodium acetate. It is used in the preparation of fruit essences and as a solvent in the manufacture of smokeless powder.

¹ *Trans. Farad. Soc.*, 1934, 30, 508.

Isoamyl acetate, amyl acetate, $\text{CH}_3\text{.CO.OC}_5\text{H}_{11}$, b.p. 138° , is used as artificial pear essence, and also as fuel in the Hefner standard lamp.

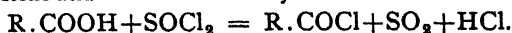
Ethyl butyrate is used as pineapple essence.

It has already been explained on p. 210 *et seq.*, that fats and waxes are for the most part esters of higher fatty acids.

2. Acid Chlorides

Acid chlorides are compounds formed by replacing the hydroxyl of an acid with chlorine, and therefore contain the group —CO.Cl .

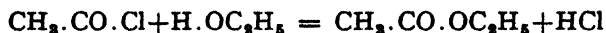
This change can be brought about by the same reactions as are used for the replacement of the hydroxyl group in alcohols, see p. 133. Acid chlorides may be prepared by the action of phosphorus trichloride or pentachloride on the acid or its alkali salts. In many cases it is more satisfactory to use thionyl chloride, when the only by-products are sulphur dioxide and hydrogen chloride, both of which are gases.



Properties.—The lower acid chlorides are colourless liquids with a sharp, irritating smell. Those of higher molecular weight are colourless crystalline compounds. They boil at a lower temperature than the corresponding acids, and generally without decomposition. In air they fume strongly, interacting with moisture to form the corresponding carboxylic acid and hydrochloric acid.



With alcohols and phenols they interact with the production of esters.



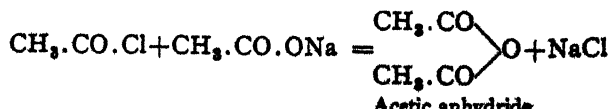
For this reason acid chlorides, especially acetyl chloride and the aromatic compound benzoyl chloride, are frequently used for detecting the presence of hydroxyl groups in an organic molecule.

They also very readily interact with ammonia and primary and secondary amines (see p. 178).

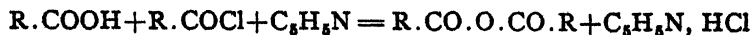
Formyl chloride, H.CO.Cl appears to be too unstable to isolate. *Acetyl chloride*, $\text{CH}_3\text{.CO.Cl}$, b.p. 55° , is manufactured by heating sulphuryl chloride (SO_2Cl_2) with sodium acetate. It is a colourless mobile liquid of pungent smell which is used to acetylate organic substances, particularly alcohols, phenols, primary and secondary alcohols.

3. Acid Anhydrides

These are prepared by the action of acid chlorides on the alkali salts of the acids.



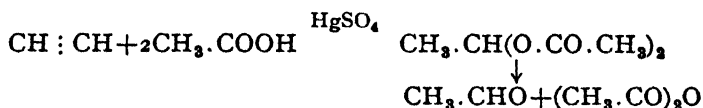
A more convenient method is by heating carboxylic acids and their chlorides in pyridine.



Acid anhydrides are liquid or solid compounds of neutral reaction, which boil at a higher temperature than the corresponding acids. They possess an unpleasant, pungent smell, and dissolve unchanged in indifferent organic solvents.

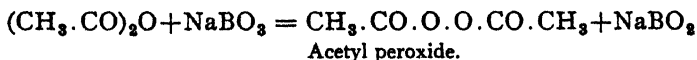
In their chemical behaviour towards water, alcohols, phenols and bases, the acid anhydrides resemble acid chlorides, except that they react far less energetically.

Acetic anhydride, $(CH_3.CO)_2O$, is a colourless liquid, b.p. 137° . It is manufactured in the United States from ketene and acetic acid (p. 203) or from *ethylidene acetate*, prepared by passing acetylene into acetic acid in presence of mercuric salts.



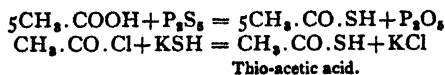
It is heavier than water and has a smell similar to that of acetic acid. Like acetyl chloride it is a valuable reagent for introducing acetyl groups into alcohols, phenols, and primary and secondary amines.

Acetyl peroxide, of importance as an accelerator in the manufacture of plastics, is prepared industrially by the action of sodium perborate on acetic anhydride.



4. Thio-acids, $R.CO.SH$

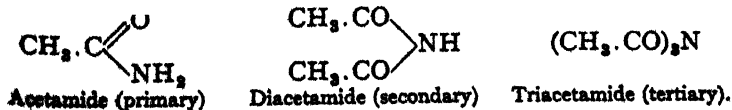
Thio-acids correspond to the thio-alcohols or mercaptans (see p. 167), and are obtained by the action of phosphorus pentasulphide on acids, or by double decomposition between acid chlorides and potassium hydrosulphide. They are liquids of nauseous odour.



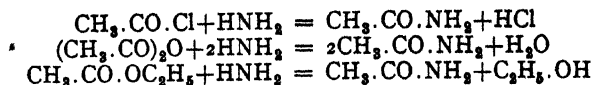
Thio-acetic acid, $CH_3.CO.SH$, is a colourless liquid boiling below 100° . It smells of acetic acid and hydrogen sulphide, and may be used for the acetylation of amines.

5. Acid Amides

It has already been seen (p. 175) that the hydrogen of ammonia can be replaced by alkyl groups to form amines. In a similar manner the hydrogen may also be exchanged for acid radicals, when *acid amides* are produced.



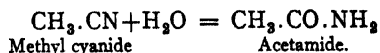
These are readily formed by the action of ammonia or amines on acid chlorides, anhydrides or esters :



They are generally prepared from the acid chloride and ammonia, but where this reaction does not proceed in the desired direction, an ester is used in place of the acid chloride.

In practice the reaction is best carried out by shaking the ester with concentrated aqueous ammonia in a closed vessel.

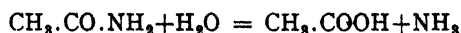
Finally, acid amides can also be obtained from nitriles (cyanides), which take up the elements of water when treated with moderately strong sulphuric acid.



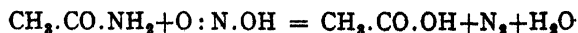
Properties.—With the exception of the fluid formamide, amides are colourless crystalline compounds, those of lower molecular weight being easily soluble in water. Their boiling-points lie considerably higher than those of the corresponding acids.

It should be noted that acid amides differ from amines in possessing very little basic character. While, therefore, the basic properties of ammonia are retained after the entrance of an alkyl group, they are very strongly diminished by the introduction of an acid radical. Salts such as $\text{CH}_3.\text{CO}.\text{NH}_2, \text{HCl}$, formed by the combination of an amide with an acid, are known, but they are very unstable and decompose into their original components on treatment with water.

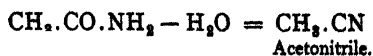
A further difference between acid amides and amines is that in the former the bond between carbon and nitrogen is easily disrupted. On boiling with water, or more rapidly on heating with alkalis, the amides are hydrolysed to the acid and ammonia.



Nitrous acid converts primary acid amides into the corresponding acids, with evolution of nitrogen. This reaction is in all respects analogous to the formation of alcohols from primary amines (p. 178).

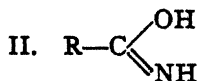
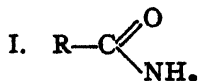


Under the influence of dehydrating agents such as P_2O_5 , SOCl_2 , etc., amides are transformed into nitriles,

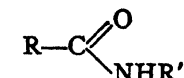


The conversion of acid amides into amines has already been described on p. 176.

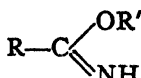
For the amides two formulæ are theoretically possible, of which formula I is generally accepted in preference to the iminohydrin structure of formula II.



Although certain metallic derivatives of the amides, such as the silver salts, appear to be related to formula II, no reactions are known which point with any degree of probability to this formula representing the constitution of the free amide.



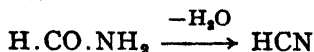
Alkylated acid amide



Imino-ether.

Formamide, $\text{H} \cdot \text{CONH}_2$, is a liquid which is readily soluble in water and alcohol.

Hydrocyanic acid is prepared on the large scale in the U.S.A. by dehydration of formamide.



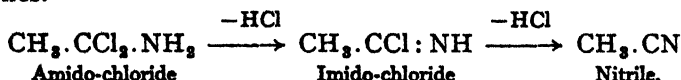
Acetamide, $\text{CH}_3 \cdot \text{CO} \cdot \text{NH}_2$, forms long needles, m.p. 82° and b.p. 222° , readily soluble in water and alcohol. It is manufactured by the action of ammonia on ethyl acetate.

6. Amido-chlorides and Imido-chlorides

Amido-chlorides are produced by the action of phosphorus pentachloride on acid amides:—



Unless the hydrogen of the amido group is substituted by alkyl radicals, these compounds are very unstable, a molecule of hydrogen chloride first splitting off to give the more stable imido-chlorides, which finally yield nitriles.



7. Hydroxamic Acids¹

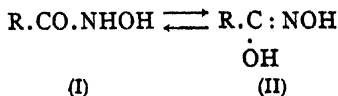
The hydroxamic acids are prepared by the action of hydroxylamine on esters. Thus *benzohydroxamic acid* is obtained from ethyl benzoate.



The hydroxamic acids are weak acids, which reduce Fehling's solution and are characterised by the intense dark blue colour they give with

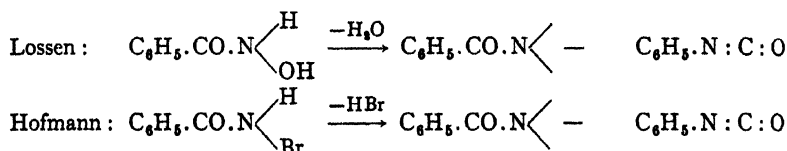
¹ H. L. Yale, *Chem. Rev.*, 1943, 33, 209.

ferric chloride. They are tautomeric substances reacting in the two forms I and II.



Only in a very few cases have both forms been isolated, but derivatives such as the diacetyl compounds of the two forms can often be obtained.

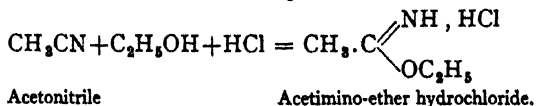
The hydroxamic acids or their derivatives undergo the *Lossen* rearrangement when heated, frequently in the presence of a base. Thus benzohydroxamic acid yields aniline and carbon dioxide and thereby resembles the Hofmann rearrangement in the migration of the phenyl radical from a carbon to a nitrogen atom. The mechanisms are very similar, an isocyanate being formed in both cases.



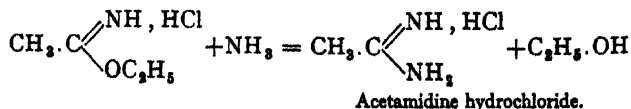
The isocyanate then undergoes hydrolysis to aniline and carbon dioxide.

8. Imino-ethers and Amidines

As has already been mentioned, the *imino-ethers* are structurally isomeric with the alkylated acid amides. They are obtained in the form of hydrochlorides when carefully dried hydrochloric acid gas is led into a solution of a nitrile dissolved in the required alcohol.



Most of these salts crystallise well, but are decomposed by water to form ammonium chloride and an ester. The free imino-ethers are liberated from the salts by treatment with alkali. They are basic liquids of peculiar smell, which are very sparingly soluble in water. Their properties differ considerably from those of the isomeric substituted amides. If the hydrochloride of an imino-ether is treated with ammonia, an *amidine salt* is formed.



The amidines are strong monacid bases, which are unstable in the free state, decomposing rapidly into ammonia and a nitrile or acid amide. The free compounds are only stable when the hydrogen attached to the nitrogen atoms is partially or completely replaced by alkyl groups.

9. Acid Hydrazides and Acid Azides

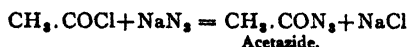
These substances were investigated more particularly by Curtius and his co-workers. The introduction of acid radicals into hydrazine results in the formation of monoacyl- or primary hydrazides, $R.CO.NH.NH_2$, and *sym.* diacyl- or secondary hydrazides, $R.CO.NH.NH.CO.R$.

Primary hydrazides are obtained by the action of hydrazine hydrate on esters, secondary *sym.* hydrazides being also formed as a by-product. The former are of a somewhat stronger basic character than acid amides and give well-defined salts. They are easily hydrolysed, and most of them reduce ammoniacal silver nitrate in the cold. Fehling's solution is only reduced on warming.

Acid azides are produced by the action of nitrous acid on primary hydrazides,



or better by interaction of an acid chloride with sodium azide in a suitable solvent such as aqueous acetone.¹

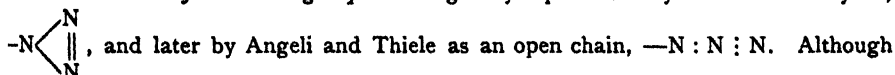


Acid azides dissolve in most organic solvents but are in general only sparingly soluble in water. In the solid state the compounds show marked differences in explosive properties. With acids and alkalis they are hydrolysed to hydrazoic acid and the parent organic acid, although some molecular rearrangement may also occur which is described in more detail below.

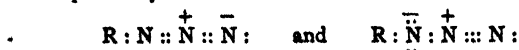
An interesting point in connection with the azides is that they offer a means of replacing the carboxyl group of an acid with the amino group, and thus of passing from an acid to an amine containing one carbon atom less (see p. 176). This process, known as the **Curtius rearrangement**, is carried out by decomposing the acid azide by heating it in a solvent. Nitrogen is evolved and the resulting organic radical rearranges itself into an isocyanate, which can in many cases be isolated. In aqueous solvents the isocyanate may suffer partial hydrolysis to amine, and this will react with unchanged isocyanate to form a substituted urea. Both isocyanate and urea, however, are converted into the amine during the final hydrolysis with hot mineral acid.



The structure of the azide group was originally represented by E. Fischer as cyclic,



in the latter formula the electronic state of the central nitrogen, with five co-valent links, is not in accordance with modern theory, later investigations of solid sodium and potassium azides by X-ray analysis² and of their solutions by Raman spectra have fully established an open chain structure. Considering the ease with which the azide ion is converted into an azide group united by a co-valent bond to carbon, and *vice versa*, it is probable that the same open structure is present in the acid azides. The difficulty presented by an individual formula of the type $R-N=N \rightleftharpoons N$ or $R-N \leftarrow N \equiv N$ is that the presence of the co-ordinate link, indicated by an arrow, should correspond to a high dipole moment, whereas the values found are only of the order 1.55. At present an azide is best regarded as a resonance hybrid between these two forms.³ In Pauling's nomenclature, in which the arrangement of the electrons is represented by dots, these forms are written respectively as



¹ See G. Powell, *J.A.C.S.*, 1929, 51, 2436. ² S. B. Hendricks and L. Pauling, *J.A.C.S.* 1925, 47, 2904; L. O. Brockway and L. Pauling, *Proc. Nat. Acad. Sci.*, 1933, 19, 860.
³ For further details see N. V. Sidgwick, *The Organic Chemistry of Nitrogen* (revised by T. W. J. Taylor and W. Baker), Clarendon Press, 1937.

Owing to their reactivity the halogenated acids are of great value in organic synthesis.

Monochloro-acetic acid, $\text{CH}_2\text{Cl}.\text{COOH}$, is prepared by passing chlorine into hot acetic acid in the presence of phosphorus, iodine, or sulphur and is obtained on the technical scale by this method. It crystallises in needles, m.p. 63° . The acid has a strong corrosive action on the skin, and therefore requires careful handling. *Dichloro-acetic acid*, $\text{CHCl}_2.\text{COOH}$, is best prepared by boiling chloral hydrate with aqueous sodium cyanide; and *trichloro-acetic acid*, $\text{CCl}_3.\text{COOH}$, by oxidation of chloral hydrate with nitric acid.

2. Esters of Nitroso- and Nitro-carboxylic Acids

Preparation.—When the nitrous gases obtained by heating arsenious oxide with nitric acid are led into esters of acyl-substituted fatty acids in the absence of solvents, a reaction occurs which leads to the removal of the acyl group (CHO , $\text{CO}.\text{CH}_3$, $\text{CO}.\text{C}_6\text{H}_5$) and the formation of nitroso derivatives of the carboxylic esters.

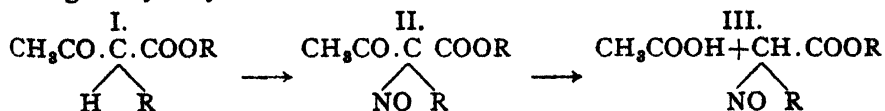
Omitting possible intermediate products, the reaction may be represented as follows:



where R represents an alkyl radical and Ac an acyl group.

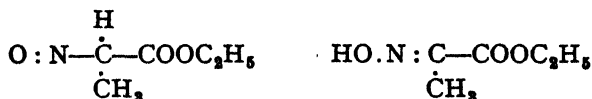
For the preparation of nitroso-carboxylic esters on a larger scale it is best to start from the corresponding acetyl derivatives, as these are well known and can generally be obtained in quantity. Methyl-acetoacetic ester, for example, is the best starting-point in the preparation of methyl-nitroso-acetic ester.

Finally, it should be noted that no replacement takes place when diethyl-acetoacetic ester is submitted to the action of nitrous gases. A necessary condition for interaction is that the carbon atom to which the acyl group is attached should also be united to an alkyl radical and a hydrogen atom. From this it may be concluded that the reaction probably takes place with the formation of an intermediate product, II, which then undergoes hydrolysis.



The *properties of nitroso-esters* are such as would be expected of true nitroso derivatives; they are blue or bluish-green oily liquids of pungent smell, which cannot be distilled without decomposition. A comparison of different alkylated nitroso-acetic esters shows that the shade of blue increases in depth as the alkyl group increases in size.

On allowing any of these compounds to stand for some time at the ordinary temperature, or more rapidly on shaking with water or alkalis, the characteristic blue colour disappears. This is partly due to intramolecular change in which the nitroso group is converted into an isonitroso group,



and partly to polymerisation, as can be shown by molecular weight determinations.

Among other properties these compounds all give the Liebermann nitroso reaction. When heated with concentrated sulphuric acid and phenol and then dissolved in water, solutions are obtained which develop a blue or green colour on being made alkaline.

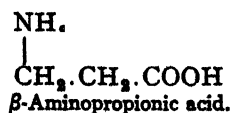
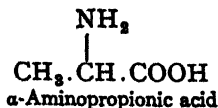
The constitution of the nitroso-compounds is proved on the one hand by their reduction to amino-esters, and on the other by their oxidation to the corresponding nitro-esters.

Esters of nitro-carboxylic acids are yellowish oils which require to be handled with great care, as they decompose on distillation and explode when rapidly heated.

Nitro-aliphatic Acids.—Nitro-acetic acid has been prepared by the action of potash on nitro-methane, methazoic acid being formed as an intermediate product. The potassium salt of nitro-acetic acid so obtained is then decomposed with dry hydrochloric acid. *Nitro-acetic acid* is stable in the dry state and crystallises in needles, m.p. 87° to 89° . When heated in larger quantities an explosive decomposition may set in.

3. Amino-acids¹

Amino-acids are acids in which hydrogen of the hydrocarbon radical is replaced by the monovalent amino group —NH_2 . They differ greatly from the corresponding acid amides, since the amino group resembles that in the amines in being firmly bound and unaffected by boiling alkalis. As in the case of the halogen acids (see p. 230), a distinction is made between α -, β -, γ -substituted acids, etc., according to the position of the substituent in the carbon chain.



The amino-acids are of great importance. Several of them are essential for life (valine, leucine, isoleucine, threonine, tryptophan, lysine, arginine

¹ H. B. Vickery and Carl L. A. Schmidt, "The History of the Discovery of the Amino-acids," *Chem. Rev.*, 1931, 9, 169; H. T. Clarke, "Natural Amino-acids," in Gilman's *Organic Chemistry*, 12, 859; Sidgwick, *Organic Chemistry of Nitrogen*, p. 105; Carl L. A. Schmidt, *The Chemistry of the Amino-acids and Proteins*; E. C. Dodds, *Chem. and Ind.*, 1950, 135.

and histidine); they have interesting properties due to their "*inner salt*" or *Zwitterion* structure (see p. 240); and the α -acids are the end-products obtained from the proteins by hydrolysis with acids, alkalis, or enzymes. The structures of some twenty-three acids obtained in this manner are now known; all have been synthesised.

Classification of α -Amino-acids

The amino-acids may conveniently be classified as follows :—

1. Aliphatic amino-acids.
2. Aromatic amino-acids.
3. Heterocyclic amino-acids.
4. Sulphur-containing amino-acids.

The first-class is subdivided into—

- (a) Monoaminomonocarboxylic acids. (Neutral amino-acids.)
- (b) Monoaminodicarboxylic acids. (Acid amino-acids.)
- (c) Diaminomonocarboxylic acids. (Basic amino-acids.)

Aliphatic Amino-acids

(a) *Aminomonocarboxylic acids.*

1. Glycine. $\text{NH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$. α -Aminoacetic acid.
2. L(+)-Alanine. $\text{CH}_3 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Aminopropionic acid.
3. L(−)-Serine. $\text{CH}_2\text{OH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Amino- β -hydroxypropionic acid.
4. L(−)-Threonine. $\text{CH}_3 \cdot \text{CHOH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Amino- β -hydroxybutyric acid.
5. L(+)-Valine. $(\text{CH}_3)_2\text{CH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Aminoisovaleric acid.
6. L(+)-Norleucine. $\text{CH}_3(\text{CH}_2)_3 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Aminocaproic acid.
7. L(−)-Leucine. $(\text{CH}_3)_2\text{CH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Aminoisocaproic acid.
8. L(+)-Isoleucine. $\begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ \text{CH}_3 \end{array} \text{CH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Amino- β -methylvaleric acid.

(b) *Monoaminodicarboxylic acids.*

These are acidic owing to the presence in the molecule of two carboxyl groups and one amino group.

9. L(−)-Aspartic acid. $\text{COOH} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. Aminosuccinic acid.
10. L(+)-Glutamic acid. $\text{COOH} \cdot (\text{CH}_2)_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Aminoglutaric acid.
11. L(+)-Hydroxyglutamic acid. $\text{COOH} \cdot \text{CH}_2 \cdot \text{CHOH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Amino- β -hydroxyglutaric acid.

(c) *Diaminomonocarboxylic acids.*

These are basic amino-acids owing to the presence of one carboxylic and two amino groups in the molecule.

12. L(+)-Lysine. $\text{NH}_2 \cdot (\text{CH}_2)_4 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α - ϵ -Diaminocaproic acid.

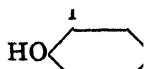
13. L(+)-Arginine $\text{NH}_2 \searrow \text{C} \cdot \text{NH} (\text{CH}_2)_3 \text{CH}(\text{NH}_2) \text{COOH}$. α -Amino- δ -guanidine-valeric acid

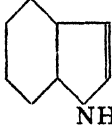
Aromatic Amino-acids

14. L(-)-Phenylalanine. $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. β -Phenyl- α -aminopropionic acid.

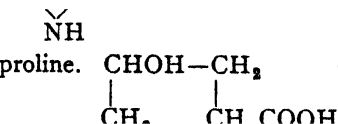
15. L(-)-Tyrosine. $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. β -*p*-Hydroxyphenyl- α -aminopropionic acid.

16. (-)-Iodogorgonic acid. $\text{HO} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. 3 : 5-Diodotyrosine.

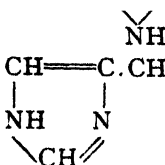
**Heterocyclic Amino-acids**

18. L(-)-Tryptophan.  $\text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. β -Indolyl- α -aminopropionic acid.

19. L(-)-Proline. $\text{CH}_2 - \text{CH}_2$ α -Pyrrolidinecarboxylic acid.



20. L(-)-Hydroxyproline. $\text{CHOH} - \text{CH}_2$ γ -Hydroxy- α -pyrrolidine carboxylic acid.

21. L(-)-Histidine.  $\text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$ β -Imidazole- α -aminopropionic acid.

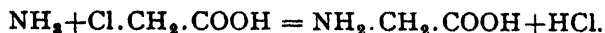
Sulphur-containing Amino-acids

22. L(-)-Cystine. $[-\text{S} \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}]_2$. Di- α -amino- β -thiopropionic acid.

23. L(-)-Methionine. $\text{CH}_3 \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. α -Amino- γ -methylthiobutyric acid.

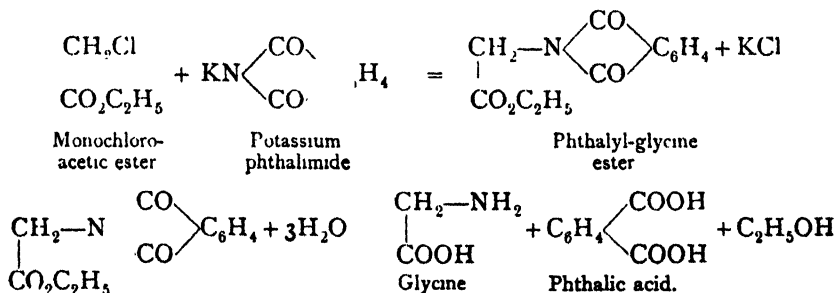
Preparation of α -Amino-acids.—It is impossible to give here all the methods used to prepare amino-acids, some of which are obtained only by tedious or unsatisfactory syntheses. A few of the more general methods are outlined.

1. Treatment of halogen-substituted acids with ammonia.



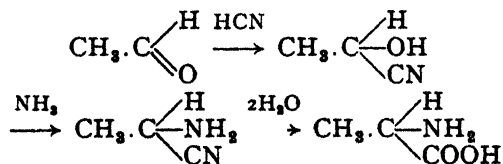
When this reaction is applied to the preparation of primary α -amino-acids, the latter may react further with yet unchanged halogen acid to form secondary and tertiary amino-acids such as $\text{NH}(\text{CH}_2 \cdot \text{COOH})_2$ and $\text{N}(\text{CH}_2 \cdot \text{COOH})_3$.

In order to avoid these side-reactions *Gabriel's method*, in which potassium phthalimide takes the place of ammonia is used. This reagent



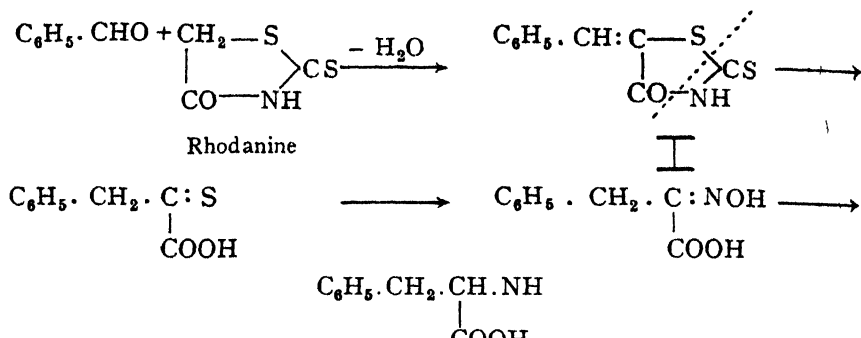
with esters of halogenated acids yields products which are first hydrolysed with sodium hydroxide, and the intermediate acid so formed, when heated with hydrochloric acid, gives phthalic acid and the amino-acid hydrochloride.

2. *Strecker's Method.* Aldehydes and ketones when treated with hydrogen cyanide yield cyanhydrins. These with ammonia are converted into amino-nitriles which on hydrolysis yield α -amino-acids.

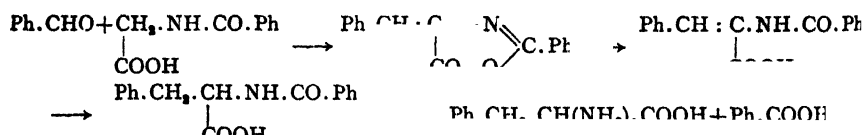


The first two phases of the above process may be combined by treating an aldehyde or ketone directly with ammonium cyanide. An even more convenient method of effecting this synthesis in the case of the sparingly soluble amino-acids is to bring equimolecular proportions of potassium cyanide and ammonium chloride into reaction with the aldehyde or ketone in aqueous or alcoholic solution. The cyanide first undergoes hydrolytic dissociation to give hydrogen cyanide and potassium hydroxide, $\text{KCN} + \text{H}_2\text{O} = \text{HCN} + \text{KOH}$. The former combines with the aldehyde or ketone to yield the cyanhydrin, which is then transformed into the amino-nitrile by the action of ammonia liberated from the free alkali and ammonium chloride.

3. Certain of the amino-acids, especially of the aromatic series, are synthesised from the products obtained by condensing aldehydes with suitable heterocyclic compounds containing reactive methylene groups. For example, rhodanine¹ condenses with benzaldehyde to give a product (I) which with alkali breaks down to an α -thioketo acid. This with hydroxylamine yields an oximino-acid which is reduced to an amino-acid.



A somewhat similar method is that of Erlenmeyer, Jun. Benzaldehyde for example, condenses with hippuric acid in the presence of acetic anhydride yielding the azlactone of benzoyl- α -aminocinnamic acid. Milk hydrolysis of the product followed by reduction gives benzoylphenylalanine.



This is easily hydrolysed by acid or alkali to DL-phenylalanine and benzoic acid.

The method is frequently used in the synthesis of more complex amino-acids, especially those with a terminal aromatic group.

4. Diaminomonocarboxylic acids are more difficult to prepare than the monoamino-acids. A promising and interesting method is the application of the Schmidt hydrazoic acid reaction (p. 176) to α -amino dicarboxylic acids when the carboxy group remote from the amino group is replaced by an amino group.² Good yields of ornithine and lysine are obtained by this method.

5. Amino-acids are prepared by hydrolysis of proteins with acids or enzymes, and various methods (see below) are employed for the separation of the individual amino-acids from the resulting mixture.

Methods of Separation.—Fischer's method is based on his observation that the ethyl esters of the monoaminomonocarboxylic acids and the

¹ Grünacher, *Helv. Chim. Acta*, 1922, 5, 610; 1923, 6, 458.
1939, 1564.

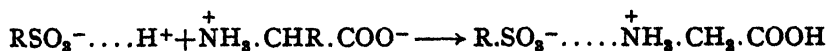
monoaminodicarboxylic acids can be distilled under reduced pressure with little or no decomposition. A rough separation can thus be effected. In Dakin's method amino-acids from protein hydrolysates are extracted from aqueous solutions with butanol. The method depends on the distribution of the amino-acids between water and butanol saturated with water. Proline and monoaminomonocarboxylic acids are extracted: the diamino- and dicarboxyl-acids remain in the aqueous layer from which they may be separated. The method has the advantage that optically active acids are not racemised during the process.

In recent years very efficient separations of amino-acid mixtures have been effected by chromatography and partition chromatography.

Amino-acids may be isolated and purified by the formation of derivatives such as copper and silver salts, picrates, picrolonates, benzoyl-compounds, etc., which are sparingly soluble in water.

The separation of the diamino-acids is best effected by precipitation with phosphotungstic acid or picric acid. In some cases almost quantitative precipitation is effected by reagents such as ammonium rhodanilate, $\text{NH}_4 [\text{Cr}(\text{CNS})_4(\text{Ph}.\text{NH}_2)_2]$, proline separating as an insoluble complex.

Ion Exchange. Dicarboxylic amino-acids can be removed from solution by basic resins, and the basic amino-acids by acidic resins. The remaining acids are then removed and concentrated by a strongly acid resin.



Other methods of separation include electro-dialysis.

Certain of the methods employed are given under the individual amino-acids—glutamic acid (p. 245), proline and hydroxyproline.

Synthetic processes such as those mentioned lead to racemic amino-acids. Resolution may be effected by fractional crystallisation of the alkaloid salts of the acylated amino-acids.

Configuration of the Amino-acids.—All the naturally occurring amino-acids with the exception of glycine are optically active. It is now generally accepted that most naturally occurring amino-acids have the same configuration, a view first expressed by Clough and later stressed by Karrer.

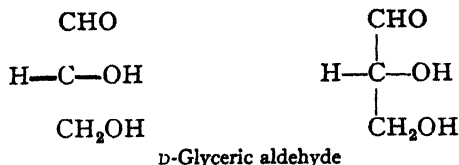
It is now possible to assign to optical isomers their absolute configurations.¹ The standard compound selected to which all other optically active substances were referred, D(+)-Glyceric aldehyde, proved to be a suitable reference compound,² not only for the sugars (see p. 301)

also for compounds such as the amino-acids. The symbols D- and L- refer to the configuration and not to the signs of rotation, which are indicated when necessary by the symbols (+) and (−) for dextro- and laevo-rotatory compounds respectively. Configurations are on this system determined by the spatial arrangement of the CHOH-group

¹ J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, 1951, 268, 271.

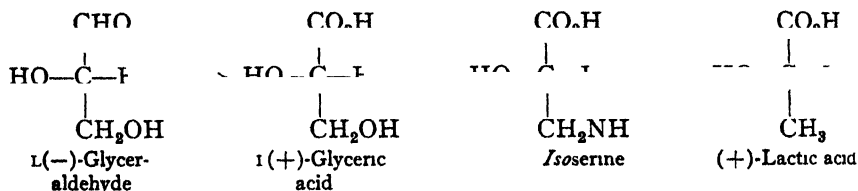
² M. A. Rosanoff, *J.A.C.S.*, 1906, 28, 114.

adjacent to the CH_2OH -group. D(+)-Glyceraldehyde possesses the absolute configuration shown below in which the thick lines denote bonds above the plane of the paper, and dotted lines bonds below this plane. The projection formula (right) is generally used.



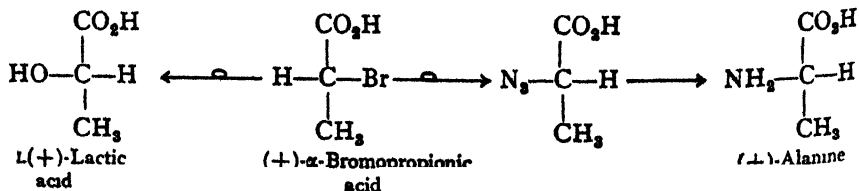
Two methods are employed to assign configurations to the amino-acids:

(1) Compounds of unknown configuration are converted into compounds of known configuration (or vice versa), care being taken to avoid Walden inversion by ensuring that the bonds of the asymmetric carbon atom are not disrupted. For example, (–)-L-glyceraldehyde is oxidised by mercuric oxide and alkali to (+)-glyceric acid which in consequence must have an L-configuration.



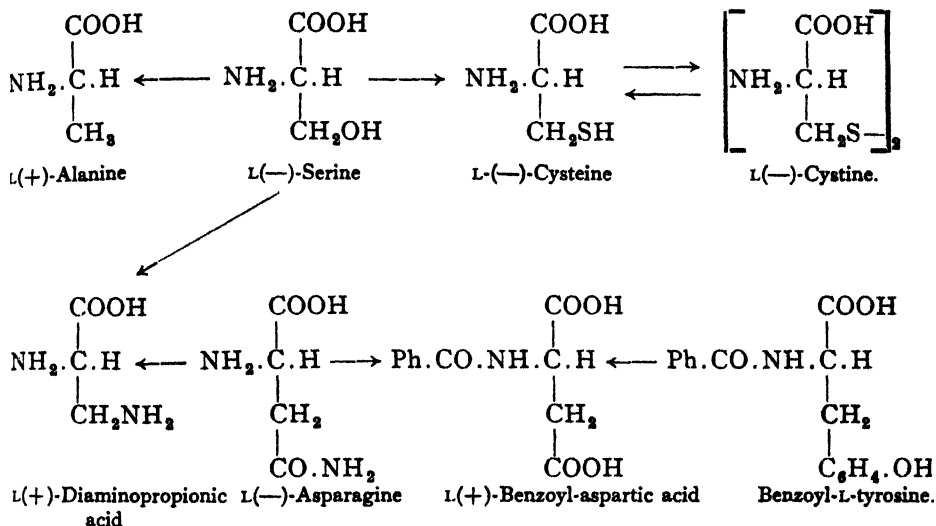
A slightly more complex instance is furnished by *isoserine* which with nitrous acid yields (+)-glyceric acid and with nitrosyl bromide followed by reduction with sodium amalgam gives (+)-lactic acid. The last-named acid must therefore have the L-configuration.

(2) In the second method compounds of unknown configuration are converted into compounds of known configuration (or vice versa), the experimental conditions being so chosen that a Walden inversion occurs (see p. 82). For example, (+)- α -bromopropionic acid undergoes alkaline hydrolysis by an $\text{S}_{\text{N}}2$ mechanism to give L(+)-lactic acid.¹ It follows that the (+)-bromo-acid has a D-configuration. Now this acid is converted into α -azidopropionic acid by an $\text{S}_{\text{N}}2$ mechanism and the azido-group reduced to give the naturally occurring (+)-alanine by Adams's method, a process which does not cleave a bond at the asymmetric centre.² (+)-Alanine must in consequence have the L-configuration.



¹ W. A. Cowdrey, E. D. Hughes and C. K. Ingold, *J.* 1937, 1208. ² P. Brewster, E. D. Hughes, C. K. Ingold and P. A. D. S. Rao, *Nature*, 1950, 166, 178.

(-)-Serine¹ can be converted into L(+)-alanine by reactions which do not involve the asymmetric carbon atom. (-)-Serine therefore has the L-configuration and is the agreed standard of reference for the configurations of the amino-acids and peptides, and with this acid as reference compound it can be shown that other naturally occurring amino-acids such as cystine,² aspartic acid,³ tyrosine,⁴ etc., have the same configuration.

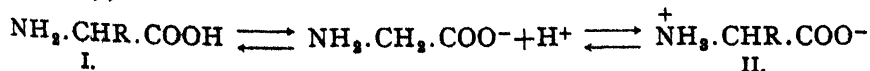


It will be noted that in this series of transformations no atom attached directly to the asymmetric carbon atom is attacked, thus avoiding Walden inversion.

Most naturally occurring α -amino-acids have been shown by similar methods to possess L-configurations.

Properties and Constitution of Amino-acids.—All the amino-acids isolated from proteins have a primary amino group in the α -position to the carboxy group, except in the case of proline and hydroxyproline when the amino group is part of the heterocyclic ring. Their melting-points are not sharp and vary with experimental conditions.

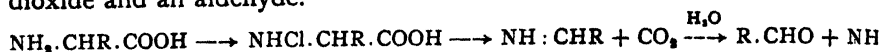
Many of the properties of the aliphatic amino-acids closely resemble those of inorganic salts such as sodium chloride. They are crystalline compounds, easily soluble in water but insoluble in alcohol and ether; their aqueous solutions are neutral or slightly acid; and they have high melting-points (230° and over). These properties combined with the absence of pronounced acidic or basic properties are not accounted for satisfactorily by formulæ representing the acids as unionised compounds (I)



¹ E. Fischer and K. Raske, *Ber.*, 1907, 40, 3717. ² E. Fischer and K. Raske, *ibid.*, 1908, 41, 893. ³ P. Karrer, *Helv. Chim. Acta*, 1923, 6, 957. ⁴ Goldschmidt and Freyss, *Ber.*, 1933, 66, 784.

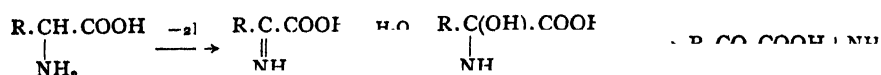
Other reactions such as *Millon's reaction* (tyrosine), *Xanthoproteic reaction* (tyrosine and tryptophane) are only given by certain amino-acids.

Action of Sodium Hypochlorite on α -Amino-acids.—Hypochlorite or Chloramine-T (sodium *p*-toluenesulphochloramide) react with α -amino acids in the same way as with primary amines, N-chloro-derivatives being formed. These products break down on warming into ammonia, carbon dioxide and an aldehyde.



Deamination, decarboxylation, and oxidation of α -amino-acids also occur in the living tissue. Among the metabolic processes three may be mentioned.

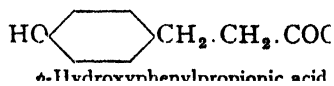
Oxidative Deamination.—Oxidation of amino-acids probably occurs in the α -position, ammonia and keto-acids being formed.



Deamination. Decarboxylation.—Both these processes occur in the intestines. Decarboxylation is probably promoted by an enzyme *carboxylase*, in the intestinal bacteria and gives rise to amines. Cadaverine for instance, is obtained from lysine.



Deamination occurs mainly in aromatic amino-acids.



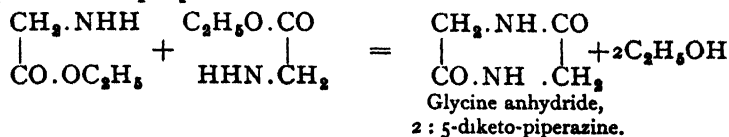
One other type of amino-acid degradation may be cited. Fermenting yeast in the presence of sugars converts amino-acids into alcohols, and the process can be used for preparing alcohols from amino-acids (p. 160). Certain moulds, such as *oidium lactis*, effect the removal of the ammonia required as nutriment in a somewhat different manner without elimination of carbon dioxide.



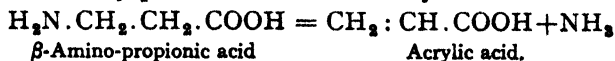
During the growth of the fungus the chain of carbon atoms remains practically unaltered, and an almost quantitative yield of α -hydroxy acid can be isolated from the solution. In this case only very small amounts of alcohol are produced. Since any desired quantity of an amino-acid may be transferred in a comparatively short time by means of *oidium lactis* we have here a convenient way of preparing optically active hydroxy acids from active or racemic amino-acids—a method which has many advantages over purely chemical processes.

Different Types of Amino-acids.—The chemical behaviour of amino-acids varies with the position of the amino group in the carbon chain.

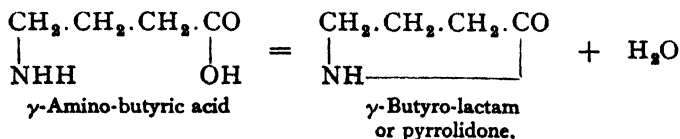
For example, *α-amino-acids* readily lose two molecules of water from two molecules of acid, or two molecules of alcohol from two molecules of amino ester, to form cyclic anhydrides called *2 : 5-diketopiperazines*. They possess the properties of acid amides.



β-Amino-acids readily part with ammonia to yield *unsaturated acids*.



γ- and δ-Amino-acids, and those with longer chains, are easily converted by loss of water into inner anhydrides termed *lactams*. These are cyclic acid amides which correspond to the lactones or cyclic anhydrides of hydroxy acids.

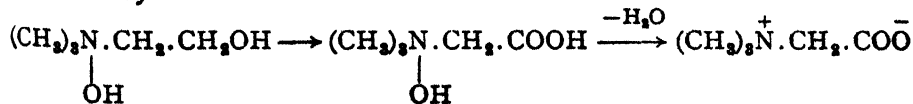


A comparison of the behaviour of the completely alkylated compounds, known as *betaines*, under the influence of heat shows even more clearly how their properties are affected by the position of the amino group (see next paragraph).

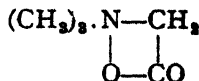
Betaines.—Fully methylated glycine can be prepared in several ways, amongst which may be cited the action of trimethylamine on chloracetic acid.



The resulting compound, *betaine* or trimethylglycine, is present in cotton-seed, in the embryo of wheat and barley, and in the sugar-beet. In the manufacture of sugar from the last source the betaine collects in the molasses. It is frequently formed with choline from which it can be obtained by oxidation.



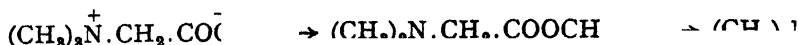
Betaine resembles glycine in its salt-like properties. It is crystalline; dissolves in water to give a neutral solution; and is insoluble in ether. With hydrochloric acid it forms a salt, $\text{Cl}(\text{CH}_3)_3\text{N} . \text{CH}_2 . \text{COOH}$, which can be titrated as a monocarboxylic acid. These properties are in harmony with the inner-salt formula given above. The older ring formula is patently incorrect. It does not account for the properties of the compound; the nitrogen is depicted as having five co-valencies; and a series of compounds of the same type, to which the general name *betaines* is now



extended, have similar properties, even though a chain of several carbon atoms separates the amino and carboxy groups.



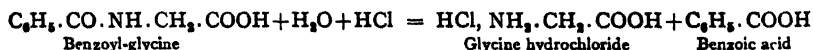
Betaine crystallises with one molecule of water, which may be removed over sulphuric acid. The anhydrous compound melts at 293° , being transformed into the methyl ester of dimethylaminoacetic acid; on further heating trimethylamine is formed. This is the basis of the technical preparation of trimethylamine by heating molasses from beet-sugar.



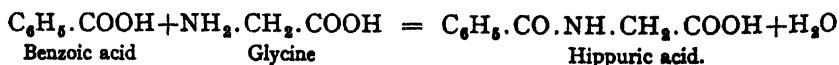
The hydrazide, $(CH_3)_3N \cdot CH_2 \cdot CONH \cdot NH_2$, trimethylaminoacetohydrazide hydrochloride,¹

prepared by the action of hydrazine on betaine esters forms water-soluble compounds with aldehydes and ketones. It is known as *Girard's Reagent I* and has been much used in the isolation of ketones of the steroids.

Glycine, *glycocoll*, *amino-acetic acid*, $NH_2 \cdot CH_2 \cdot COOH$, melts in the region 220° - 235° . It may be prepared either by boiling glue with dilute sulphuric acid or baryta (hence its name), or from its benzoyl derivative, *hippuric acid*, which occurs in the urine of horses, by hydrolysis with hydrochloric acid.



Many compounds such as benzoic acid are eliminated from the human organism as hippuric acid or substituted hippuric acid, glycine (synthesised in the body for the purpose) combining with the benzoic acid to form hippuric acid.



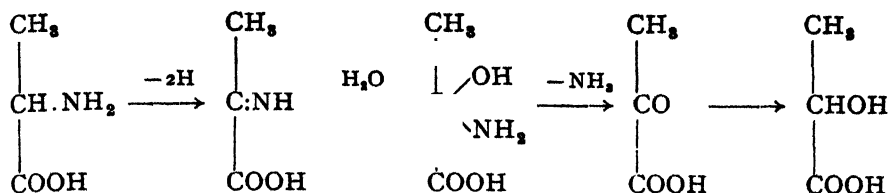
Toluene is eliminated as hippuric acid and xylene as a methylhippuric acid. Benzene with no oxidisable side-chain cannot be eliminated in this way, but is removed by a much slower process. Benzene is therefore more toxic than toluene or xylene.

Methylglycine, *sarcosine*, $CH_3 \cdot NH \cdot CH_2 \cdot COOH$, is obtained from creatine (p. 356).

α -Alanine, $CH_3 \cdot CH(NH_2) \cdot COOH$, is obtained by the hydrolysis of silk or from α -chloro- or α -bromo-propionic acid and ammonia. On treatment with nitrous acid it is converted into lactic acid (p. 238).

¹ Girard and Sandulesco. *Helv.* 1926, 29, 1000

Transitions between alanine and lactic acid also occur in the human organism, pyruvic acid being an intermediate compound.

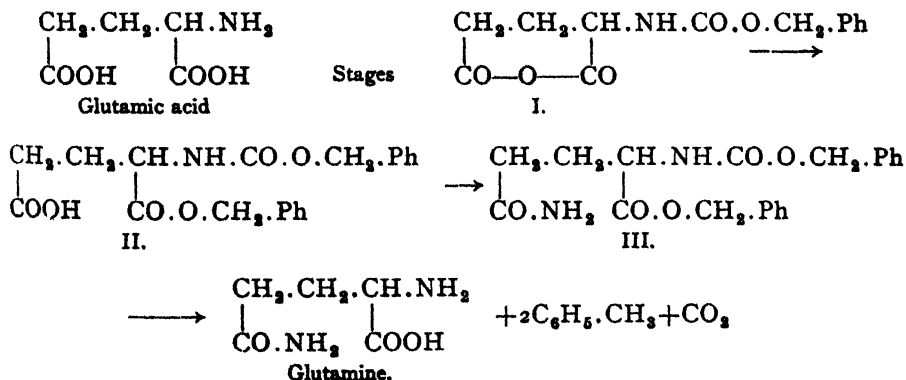


From its relationship to L-glyceraldehyde (see p. 237), the natural alanine is more correctly described as L-alanine (compare sugars, p. 302).

L-Leucine occurs in the pancreas and spleen. It is noteworthy that while the *dextro*-rotatory acid has a sweet taste, the *laevo*-isomer has a bitter taste.

Aspartic Acid and Asparagine.—Aspartic acid probably exists in the protein molecule as the amide, asparagine.

Glutamic acid, probably is present in proteins as its amide, *glutamine*, which may be prepared in the laboratory by the elegant method of Bergmann.¹ Carbobenzoxy chloride (prepared from benzyl alcohol and phosgene), $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{O}\cdot\text{CO}\cdot\text{Cl}$, reacts readily with the amino group in amino-acids to give carbobenzoxy-derivatives. The acid with the amino group thus protected may then be converted into various derivatives. The value of the method rests on the fact that the carbo-



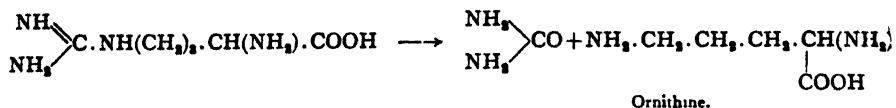
benzoxy group can finally be removed at room temperature, thus avoiding the use of reagents which might destroy amide or peptide linkages or racemise the compound. For example, carbobenzoxy-glutamic acid on boiling with acetic anhydride is converted into an anhydride I which with benzyl alcohol gives a benzyl ester II, the carboxy group remote from the amino group being unattacked. The free carboxy group is then converted into the amide III, which on catalytic hydrogenation gives toluene,

¹ M. Bergmann and L. Zervas, *Ber.*, 1932, 65, 1192; *ibid.*, 1933, 66, 1288.

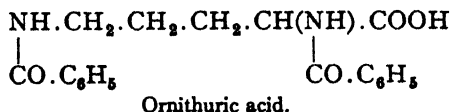
carbon dioxide and glutamine. The method is of great value in peptide synthesis.

Arginine, $\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \cdot \text{NH}(\text{CH}_2)_3 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH} \\ \diagdown \\ \text{NH}_2 \end{array}$, is found among

the hydrolytic products of many animal proteins and is also contained in the cotyledons of etiolated lupins; also in the protamines of fish sperm. Its properties are affected by the strongly basic guanidino group. It is hydrolysed to ornithine and urea by the enzyme, *arginase*.



Ornithine, $\text{NH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$, appears not to be one of the constituents of proteins. It is used by fowls for the detoxication of benzoic acid, the dibenzoyl derivative of ornithine, *ornithuric acid* being formed.



Hydroxy-, thio-, dibasic and cyclic amino-acids are described under their appropriate headings.

PEPTIDES¹

Mineral acids disrupt proteins to give as final products α -amino-acids, but less drastic treatment by the use of enzymes yields intermediate products—*albumoses*, *peptones*, *peptides*—which are differentiated chiefly by means of their colloidal properties.

Proteins \longrightarrow Albumoses \longrightarrow Peptones \longrightarrow Peptides \longrightarrow Amino-acids

The peptones are generally considered to be the last breakdown products which still possess true protein characteristics, but, as the higher peptides resemble the proteins in many respects, they have been studied intensively. In connection with these compounds Fischer wrote: "The higher members of this synthetic series are, with respect to their external properties, certain colour reactions, and behaviour towards acids, alkalis and ferments, so similar to the natural peptones that they may be considered as their nearest relatives, and I regard their synthesis as the first step in the production of natural peptones and albumoses." Not only is the synthesis of peptides a necessary prelude to that of the proteins, but the behaviour of the peptides towards enzymes furnishes valuable information regarding the action of proteolytic enzymes.

Many polypeptides have been synthesised. Emil Fischer was the first to develop methods by which the molecules of various amino-acids could be successively linked on to one another in a species of amide

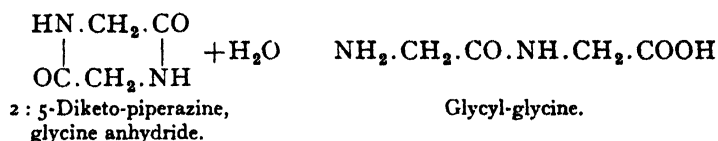
¹ *Naturally Occurring Peptides*, by R. L. M. Synge, *Quart. Rev.*, 1949, 3, 245.

formation, each intermediate substance being isolated and identified. The resulting products, the simplest representative of which is *glycyl-glycine*, $\text{NH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\cdot\text{COOH}$, obtained from glycine, are described under the collective name of **peptides**. According to the number of amino-acid residues contained in the molecule, they are distinguished as *di*-, *tri*-, *tetra*-peptides, and so on.

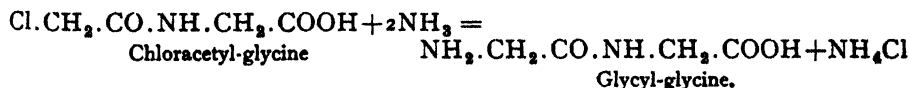
Synthesis of Peptides

1. Dipeptides can be prepared by the hydrolysis of 2:5-diketo-piperazines which, as stated on p. 243, are obtained from α -amino-acids by loss of 2 mols. water, or from the corresponding esters by loss of 2 mols. alcohol.

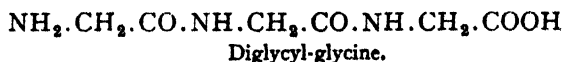
Glycine anhydride, the simplest 2:5-diketo-piperazine, formed the starting-point of Fischer's investigations. When this compound is boiled for a short time with concentrated hydrochloric acid or shaken with cold dilute alkali, the ring is opened and a hydrochloride or salt of *glycyl-glycine* is obtained.



2. Polypeptides are obtained by bringing amino-acids or their esters into reaction with halogen-substituted acid chlorides, and treating the product with ammonia. For example, *chloracetyl-chloride* $\text{ClCH}_2\cdot\text{COCl}$ reacts with glycine to give *chloracetyl-glycine*, which with ammonia yields *glycyl-glycine*.



Glycyl-glycine may be then combined with a second molecule of *chloracetyl-chloride* and the product treated with ammonia, when the tripeptide *diglycyl-glycine* is obtained.

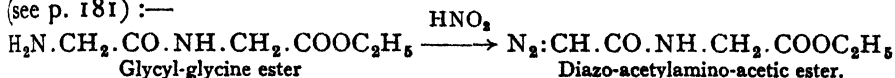


Most of the polypeptides at present known have been obtained by this method or modifications such as the following in which the acid chloride of a halogeno-amino-acid is made to couple up with esters of amino-acids or polypeptides. Thus the chloride of *chloroacetyl-glycine* condenses with the ethyl ester of alanine to give a product which may

Properties of the Peptides

The polypeptides are solid substances which generally dissolve readily in water but very sparingly in alcohol; most of them melt with decomposition at a temperature above 200°. In these properties they resemble the amino-acids, and probably, like the latter, have a *Zwitterion* structure. Whereas most of the α -amino-acids have a sweet taste, the polypeptides are slightly bitter (or insipid), therein resembling the natural peptones. Synthetic polypeptides may be hydrolysed in much the same way as peptones or proteins. On boiling with concentrated hydrochloric acid they are completely decomposed into amino-acids, but alkalis only attack them slowly, particularly at ordinary temperatures. The $-\text{CO}.\text{NH}-$ group present in all peptides is known as the *peptide linkage* and it is this bond that is broken on hydrolysis.

The amino and carboxy groups in the polypeptides are capable of undergoing the same reactions as in the amino-acids. For instance, the polyglycine esters yield diazo-esters on treatment with nitrous acid (see p. 181):—



Esters of polypeptides are much more easily purified and identified than the parent compounds, and may be used for the synthesis of more complex polypeptides. They may be prepared just as readily as these of the amino-acids by the use of alcoholic hydrochloric acid. Esters of the dipeptides are comparatively easily converted into diketopiperazines (see p. 243) on treatment with alcoholic ammonia.

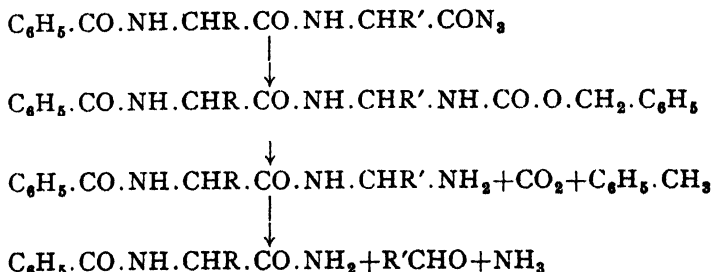
It has already been stated that in many ways the properties of the synthetic peptides resemble those of the proteins. Many tripeptides and all the higher polypeptides give the biuret test, and the higher polypeptides are precipitated by reagents such as phosphotungstic acid, tannic acid, etc., and certain colour tests are given when particular amino-acid residues (tyrosine, etc.) are present in the peptide. The most striking similarity, however, is found in the hydrolysis to amino-acids, which is catalysed not only by acids and bases but also by those enzymes responsible for the hydrolysis of proteins. Such similarities led E. Fischer to postulate that proteins are long-chain polypeptides of high molecular weight with, of course, the characteristic peptide linkage. With certain modifications this structure of the protein molecule is generally accepted.

Structure of the Polypeptides.—The structure of the polypeptides may be determined either by synthesis (p. 247) or by degradation experiments. They react with naphthalene-sulphonic chloride to give derivatives which are disrupted by dilute hydrochloric acid, the peptide link being broken, while the more stable bond between the naphthalene-sulphonic group and the amino group remains intact, e.g.



This method, though useful, is limited to identifying the amino-acid attached to the beginning of the peptide chain.

A more general method is that of Bergmann,¹ by which amino-acids are removed one by one from the peptide. The carboxy group of the benzoylated peptide is converted to the azide which with benzyl alcohol gives the carbobenzoxy-derivative. This is hydrogenated, and the amino compound so obtained on hydrolysis gives an aldehyde and the amide of a peptide containing one less amino-acid residue.



Identification of the aldehyde determines the nature of the end group of the peptide and the process may be repeated.

Partition chromatography is now playing an important part in the determination of peptide structure and this is well illustrated by Synge's work² on *Gramicidin S*, (Soviet Gramicidin), a crystalline antibiotic discovered by the Russians and used by them in the treatment of war wounds. Synge showed that it is a polypeptide composed of L-ornithine, L-proline, L-valine, L-leucine, and D-phenylalanine. The arrangement of the amino-acids was shown by two-dimensional chromatographic separation into di- and tri-peptides. The constitution of these was found by hydrolysis into the component amino-acids.

Dipeptides	Tripeptides
valyl-ornithine	valyl-ornithyl-leucine
ornithyl-leucine	leucyl-phenylalanine
leucyl-phenylalanine	phenylalanyl-proline

These results can be reconciled only with the following amino-acid sequence in the peptide.

.....valine-ornithine-leucine-phenylalanine-proline

The "true" molecule is a closed peptide chain.

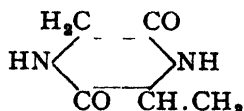
Polypeptides as Breakdown Products of Proteins.—Di- and tri-peptides have been isolated by various investigators from the products of hydrolysis of proteins. Glycyl-alanine was isolated in the form of the α -naphthalene-sulphonic derivative and its structure confirmed by hydrolysing the latter to alanine and naphthalene sulphoglycine. This reaction illustrates the utility of the naphthalene-sulphonic derivatives in determining the

¹ M. Bergmann and L. Zervas, *J. Biol. Chem.*, 1936, 113, 341.
Biochem. J., 1945, 39, 262.

² R. L. M. Synge,

structure of polypeptides. The isolation of these compounds is evidence of a common link between polypeptide synthesis and protein disruption.

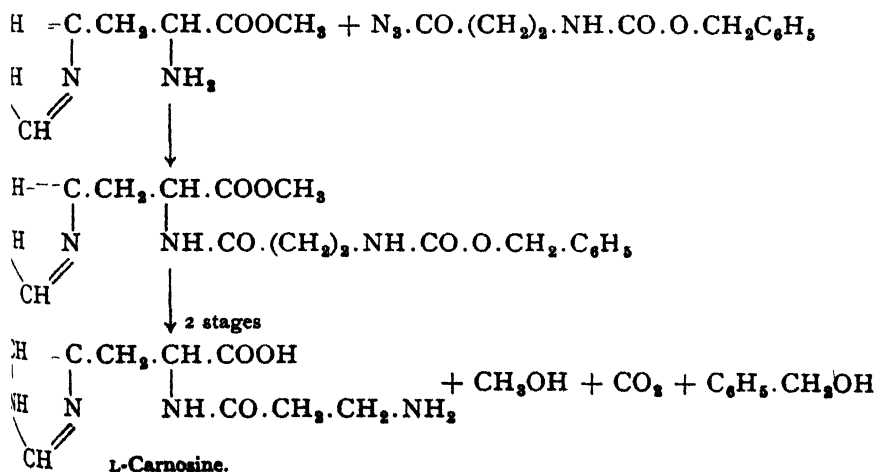
Among the peptides isolated from proteins are: *alanyl-leucine* (from elastin), *leucyl-glutamic acid* (from gliadin), *glycine-proline anhydride* (from gelatine), and *isoleucyl-valine anhydride* (from caseinogen). *Methyl-diketo-piperazine*,



is found among the hydrolysis products of silk fibroin. It is identical with the synthetic compound from glycine and alanine.

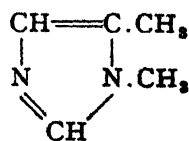
Two dipeptides—*carnosine* and *anserine*—and a tripeptide—*glutathione*—are of biological importance and call for mention.

The water-soluble dipeptide *L-carnosine*, which occurs in muscle has been shown to be β -alanylhistidine, since *L*-histidine is obtained by alkaline hydrolysis, while acid hydrolysis of the phenylureide yields the phenylureide of β -amino-propionic acid. It has been synthesised¹ from the azide of carbobenzoxy- β -alanine and the methyl ester of histidine. The methyl group is removed by hydrolysis, and the carbobenzoxy group in the usual way by catalytic hydrogenation (*cf.* p. 245).



A methyl derivative of carnosine, *anserine*, has been isolated from the muscles of certain birds and fish. Hydrolysis of anserine gives alanine and a methyl-histidine, and heating with soda yields 1:5-dimethylimidazole, thus establishing the position of the methyl group.

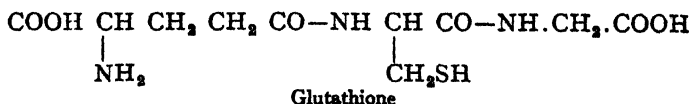
Of special interest is the tripeptide *glutathione* isolated by Hopkins and shown to be present in the majority of cells. It plays an important part in physiological oxidations.



Glutathione

¹ Sifferd and du Vigneaud, *J. Biol. Chem.*, 1929, 83, 1.

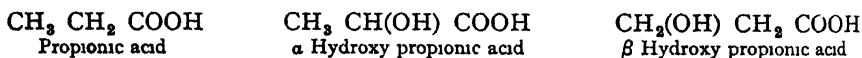
is a tripeptide built up of the three amino-acids, glycine, glutamic acid and cysteine.



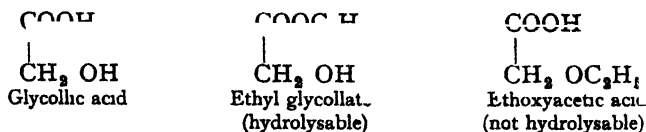
4. Hydroxy-acids of the Aliphatic Series

Nomenclature.—The hydroxy-acids are derived from the fatty acids by replacing a hydrogen atom of the hydrocarbon radical by a hydroxyl group. They are designated by prefixing "hydroxy" to the name of the corresponding fatty acid; for example, $\text{HO} \cdot \text{CH}_2 \cdot \text{COOH}$ is *hydroxy-acetic acid*. They may also be considered to be oxidation products of the polyhydric alcohols, as expressed in the above case by the term *glycollic acid*.

Among the hydroxy-acids we have the same possibilities of isomerism as in the case of the chloro- and amino-acids. Similarly, the position of the substituent with regard to the carboxyl group is represented by the use of letters, *e g*,



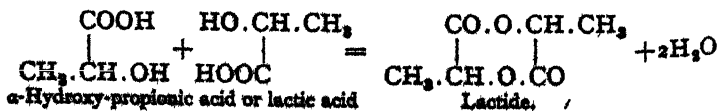
Properties.—The hydroxy-acids possess the characteristics of both alcohols and acids. Thus the presence of the carboxyl group leads to the formation of salts, esters and amides, and the hydrogen of the alcoholic hydroxyl group is also replaceable by alkali metals and alkyl or acyl radicals.



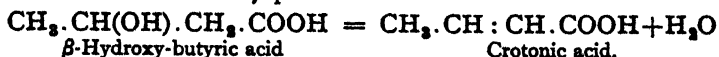
The strength of the fatty acids is increased by the entrance of the hydroxyl group into the molecule, the effect being the greater the closer the hydroxyl stands to the carboxyl group. This is shown by a comparison of the dissociation constants of the acids.

The influence exerted by the position of the hydroxyl group is also clearly illustrated in the different manner in which water is eliminated from α -, β - and γ -hydroxy-acids.

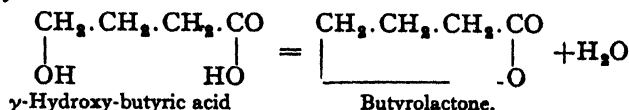
α -Hydroxy-acids, on being heated, lose water in such a way that two molecules of the acid interact, the hydroxyl group of each uniting with the carboxyl group of the other molecule to form cyclic *dilactones* (p. 255) known as *lactides*. In the process each molecule of lactic acid is esterified by the other.



β -Hydroxy-acids, when heated by themselves or with dilute sulphuric acid, generally decompose into water and unsaturated acids, the water being formed by combination of the hydroxyl group with the adjacent hydrogen atom in the α - or γ -position.



The γ - and δ -hydroxy-acids readily eliminate water, even when in solution at the ordinary temperature, and are transformed into simple cyclic anhydrides called *lactones*.

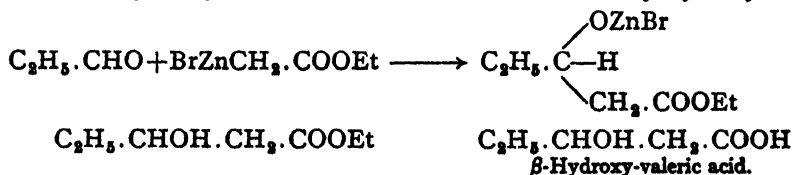


Methods of Formation.—Hydroxy-acids may be obtained by the following methods :—

1. From halogen-substituted fatty acids by heating with water.



2. β -Hydroxy-acids are prepared by the interaction of α -halogeno esters on aldehydes or ketones in presence of zinc (*Reformatsky reaction*). Organozinc halides are undoubtedly formed and react with the carbonyl compounds in a manner similar to that of the Grignard reagents. The zinc complex so formed is decomposed by dilute sulphuric acid to give the ester of a β -hydroxy-acid. The free acid is obtained by hydrolysis.

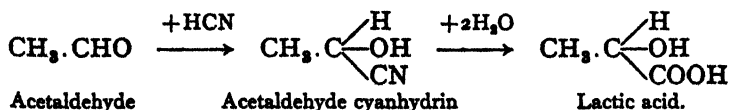


In the above example, propionic aldehyde, ethyl bromacetate, and zinc yield β -hydroxy-valeric acid.

3. By the reduction of aldehydic or ketonic acids.

4. From amino-acids by interaction with nitrous acid (*cf.* p. 245).

5. By the addition of hydrogen cyanide to aldehydes or ketones and hydrolysis of the cyanhydrins so formed :



The best known and most important of the hydroxy-acids are glycollic acid and ordinary or fermentation lactic acid.

Glycollic acid, hydroxy-acetic acid, $\text{CH}_2\text{OH} \cdot \text{COOH}$, may be prepared by heating acetic acid with water. It occurs in the green leaves of the wild vine and in unripe

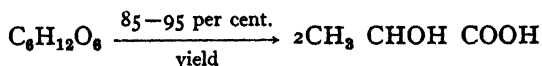
When distilled *in vacuo*, water is given off and glycollide, $\text{O} \begin{array}{c} \diagup \text{CO} \cdot \text{CH}_2 \\ \diagdown \text{CH}_2 \cdot \text{CO} \end{array} \text{O}$, is formed.

SUBSTITUTED CARBOXYLIC ACID

Lactic Acids, $C_3H_6O_3$

Lactic acids are monohydroxy derivatives of propionic acid, $CH_3 \cdot CH_2 \cdot COOH$. It will be seen at once that two structural isomerides are possible, according as the hydroxy group occupies the α - or β -position. Of these, α -hydroxy-propionic acid or ordinary lactic acid, which exists in optically active modifications, is of special interest from the theoretical as well as the practical standpoint. The researches on the lactic acids published in 1873 by Wislicenus, led him to the conclusion that differences between isomeric compounds having the same structural formula could only be accounted for by a different position of their atoms in space a view similar to that advanced some time previously by Pasteur from his investigation into the tartaric acids. These two pieces of work formed the foundation of the theory of stereoisomerism put forward shortly afterwards by Le Bel and van't Hoff independently.

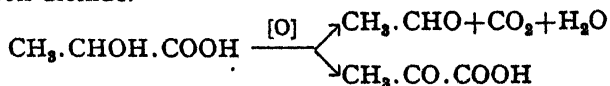
Lactic acid, *racemic α -hydroxypropionic acid*, is obtained commercially by the fermentation of molasses or starch hydrolysates with various strains of the *lactobacillus* family.



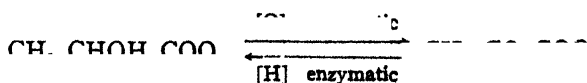
The formation of lactic acid in sour milk is a consequence of this process. Buchner and Meisenheimer showed that this action, like that of alcoholic fermentation, is caused by an enzyme produced in the living micro-organism, which can be separated from living cells without losing its activity.

Lactic acid is one of the oldest known acids and is widely distributed in nature. It is the main constituent of sour milk (hence its name) and is found in the blood and muscle of animals. In recent years it has been used on a considerable scale in the manufacture of plastics.

The structure of lactic acid follows from its synthesis (p. 253) and from its chemical behaviour. Like other α -hydroxy acids lactic acid is rapidly oxidised at room temperature by potassium permanganate with loss of carbon dioxide.



It may also be oxidised to pyruvic acid. The corresponding enzymatic oxidation of lactate ion to pyruvate ion is of great biochemical significance.



These oxidations establish the presence in the molecule of the $CH_3 \cdot CHOH$ group. The carboxyl group behaves as expected and gives rise to sodium salts, esters, etc.

As may be seen from its formula, α -hydroxypropionic acid contains an *asymmetric carbon atom*. According to theory it should therefore exist in three stereoisomeric forms, viz., a dextro- and a lævo-modification, and a racemic compound composed of equal amounts of these two (see p. 26). All three are known. The lactic acid of commerce is the racemic form, being optically inactive and capable of separation into its active components by any of the usual methods (p. 33). It is difficult to prepare in the crystalline state and is usually obtained as a viscous liquid.

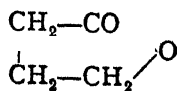
Sarco-lactic acid, is the dextro modification of α -hydroxypropionic acid and has the L-configuration (see p. 237). It is therefore fully described by the name L(+)-lactic acid. It is the form occurring in blood and is most conveniently prepared from Liebig's extract of meat.

L-lactic acid is the first recognisable degradation product of glucose, the presence of which can be traced in the body; under favourable conditions of concentration in the liver it may be reconverted into glucose. In the muscles it appears to be formed from carbohydrate-phosphoric acid compounds, one of which has been isolated from fresh muscle.

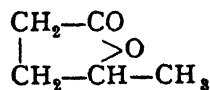
Lactones

Nomenclature.—As already stated on p. 253, the inner esters of hydroxy-acids, formed by splitting off a molecule of water between the carboxyl and the hydroxyl groups, are known as lactones. They are formed particularly easily by γ - and δ -hydroxy-acids, which yield γ - and δ -lactones respectively. A few α -, β - and ϵ -lactones are also known.

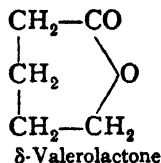
The various compounds are distinguished by use of Greek letters or numbers representing the relative positions of the carboxyl and hydroxyl groups.



γ -Butyrolactone



γ -Valerolactone



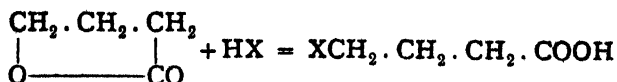
δ -Valerolactone

Many lactones such as coumarin and its derivatives occur in nature, while others, including the cardiac glycosides, are physiologically active.

Formation.—Reactions leading to the formation of lactones depend in most cases on the elimination of water from hydroxy acids, or of hydrogen halide from halogen-substituted acids, in which the hydroxyl or halogen occupies the position corresponding to the particular lactone required.

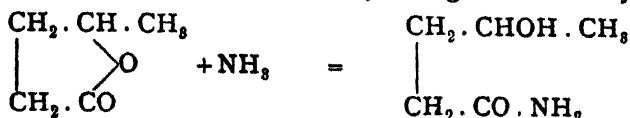
1. The majority of γ -hydroxy-acids part with water immediately at the ordinary temperature, even in aqueous solution, and cannot therefore be isolated as such. But lactone formation resembles esterification in being a reversible reaction; consequently the change is never complete

acids. In this way γ -chloro-, bromo- and iodobutyric acids are readily obtained from butyrolactone.



Although lactones are not attacked in the cold by alkali carbonates, they are hydrolysed like all esters by free alkalis, with the formation of salts of the corresponding hydroxy- or keto-acids.

Lactones also unite with ammonia, yielding amides of hydroxy-acids



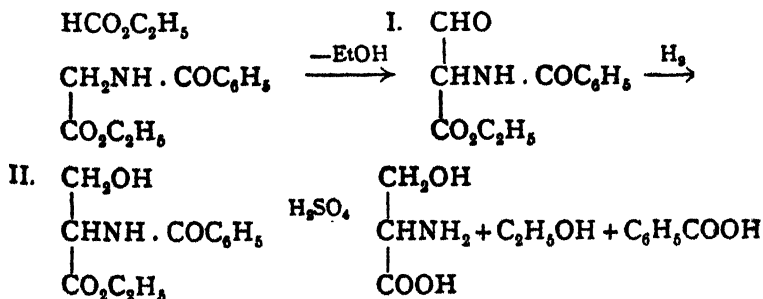
and with hydrazine hydrate and phenylhydrazine to form hydrazides.

By the use of sodium amalgam in weakly acid solution, lactones of poly-hydroxy acids may be reduced to the corresponding aldoses, a reaction which is of great value in the synthesis of sugars.

5. Hydroxy-Amino-Acids

The hydroxy-amino-acids, like α -amino- and diamino-acids, are of importance in the chemistry of the proteins. One of the simplest and best known examples of this type is *serine*, obtained as a hydrolysis product of sericin or silk gum.

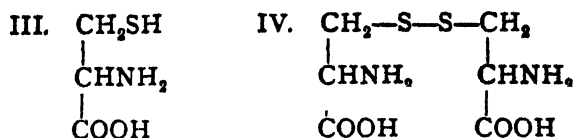
Serine, α -amino- β -hydroxy-propionic acid, $\text{CH}_2\text{OH} \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$ was discovered in 1865 by Cramer among the hydrolysis products of sericin or silk gum, and is of special interest from the chemical as well as the physiological standpoint as being the simplest and first known hydroxy-amino-acid of the aliphatic series. A synthesis, which permits of the preparation of serine from readily available starting materials, was effected by Erlenmeyer, jun. It consists in the condensation of



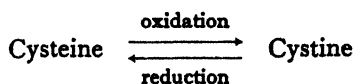
formic ester with hippuric ester, to give *formyl-hippuric ester* I. This product is then reduced to *benzoyl-serine ester* II, which on hydrolysis with very dilute sulphuric acid yields serine, benzoic acid and alcohol.

L-Serine is the natural product as found in proteins, and has been isolated from silk. On reduction with hydriodic acid and phosphorus, serine is converted into alanine.

Cysteine III and **cystine IV** are two acids standing in close relationship to serine. Cysteine is a thio-serine and cystine the corresponding



disulphide. They occur in most proteins, but only in traces in gelatine. Erlenmeyer, jun., prepared cysteine synthetically from benzoyl-serine ester by heating it with P_2S_5 and decomposing the product with concentrated hydrochloric acid. Cysteine on gentle oxidation by air is transformed into cystine; cystine, on the other hand, is readily reduced in acid solution to cysteine.



The reversible dehydrogenation of cysteine to cystine plays a fundamental part in the oxidation processes which occur in living tissues (cf. p. 251).

The constitution of cysteine was originally confirmed by its conversion into taurine (see p. 264). This relationship is also of significance in the living organism, since cysteine is the parent substance of taurine, which forms one component of an important bile acid, *taurocholic acid*, found in ox-gall. Cysteine is transformed into taurine by decarboxylation followed by oxidation: $\text{HS}\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH} \longrightarrow \text{HO}_2\text{S}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$.

Methionine is the only other known sulphur compound entering into protein structure. It acts as a methylating agent in certain biochemical reactions and is one of the ten amino acids essential for the growth and repair of animal tissue. Methionine was synthesised by Barger¹ and shown to be *γ-methylthiol-α-amino-butyric acid*, $\text{CH}_3\text{S}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}$. A new commercial synthesis in the United States makes the acid available at a fraction of the previous cost.

XII

Polyhydric Alcohols

In addition to the monohydric alcohols already described (p. 146), polyhydric alcohols are known containing two or more hydroxyl groups in the molecule. Only in rare cases are more than one of these groups found attached to the same carbon atom. Polyhydric alcohols usually undergo all the reactions quoted under monohydric alcohols, although,

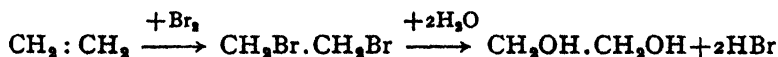
¹ Barger and Coyne, *Biochem. J.*, 1928, 22, 1417. Barger and Weichselbaum, *Biochem. J.*, 1931, 25, 997. The acid was first isolated by J. Mueller (*J. Biol. Chem.*, 1923, 56, 157).

as would be expected, the changes suffered by virtue of the single hydroxyl grouping may be repeated several times in the case of the polyhydric compounds. Derivatives may thus be formed which, like hydroxy-acids and amino-alcohols, contain more than one typical class-group in the molecule. These compounds generally possess the characteristics of both of the classes they represent.

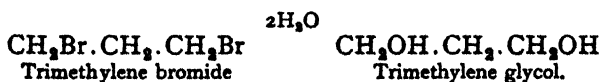
1.—DIHYDRIC ALCOHOLS OR GLYCOLS, AND THEIR DERIVATIVES

Dihydric alcohols take their name from glycol, the simplest member of the series, and may be derived from hydrocarbons by replacing two hydrogen atoms, attached to different carbon atoms, by hydroxyl groups. They are distinguished as α -, β -, γ - or δ -glycols, according as the hydroxyl groups stand in the 1 : 2, 1 : 3, 1 : 4, or 1 : 5 positions to one another.

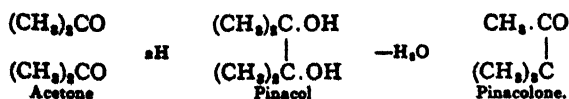
Methods of Formation.—Dihydric alcohols may be obtained in the same manner as the mono-substituted compounds from the corresponding halogen derivatives, by heating them with water or potassium carbonate, or from chlorhydrins and sodium bicarbonate. The former reaction is of special importance for the preparation of α -glycols, since the corresponding 1 : 2-dibromides are readily obtained by the addition of bromine to olefins. In this way glycol was first prepared by Würtz.



Other glycols may be obtained in a similar manner. For example, allyl bromide combines with hydrobromic acid to form trimethylene bromide, which may readily be converted into trimethylene glycol.



It has already been mentioned on p. 124 that α -glycols are formed by the cautious oxidation of olefins with aqueous potassium permanganate. They are also produced, together with secondary alcohols, when ketones are reduced electrolytically or by means of sodium. Under these conditions acetone yields isopropyl alcohol and pinacol (tetramethyl-ethylene glycol, formerly known as *pinacone*). The latter on treatment with dilute sulphuric or hydrochloric acid undergoes a remarkable intramolecular rearrangement with elimination of water to form pinacolone (originally *pinacolone*).

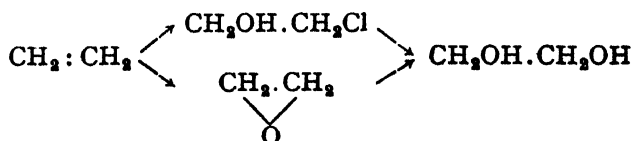


In a similar manner, by the reduction of various ketones, a number of tetra-alkylated ethyleneglycols have been prepared, which are classed as pinacols and show the same behaviour with dilute mineral acids as pinacol itself.

Properties.—Glycols are generally viscous, colourless and sweet-tasting liquids (hence the name), which are easily soluble in water and alcohol but difficultly soluble in ether. Their boiling-points lie considerably higher than those of the monohydric alcohols with a similar carbon chain.

The chemical behaviour of the glycols may be deduced from that of the simple alcohols. This will be evident when the properties of ethylene glycol are discussed (see below).

Ethylene glycol, glycol, $\text{CH}_2\text{OH}.\text{CH}_2\text{OH}$, may be formed according to the methods already described. Technically, it is used in large quantities for mixing with water to prevent freezing (*anti-freeze*), *e.g.*, in radiators of motor cars. For this purpose it is prepared either from ethylene chlorhydrin or ethylene oxide, both of which are obtained from ethylene—a by-product of petroleum “cracking” processes.



Glycol is an oily, colourless liquid, b.p. 197.5° and sp. gr. 1.125, which is miscible with water and alcohol but only dissolves sparingly in ether. Ethylene glycol exhibits many of the properties of a primary alcohol. The hydroxyl groups may be replaced by halogen, or its hydrogen atoms replaced by alkyl or acyl groups, or by alkali metals. Since, however, it contains two hydroxyl groups in the molecule, it is obvious that these reactions may take place in two stages. Thus oxidation yields glycollic acid and finally oxalic acid. Phosphorus pentachloride gives the neutral hydrochloric acid ester, $\text{CH}_2\text{Cl}.\text{CH}_2\text{Cl}$, which may also be considered as a dichloro-substitution product of ethane. On the other hand when heated with hydrogen chloride or bromide only one hydroxyl group is replaced by halogen, with the production of chlorohydrins and bromohydrins.

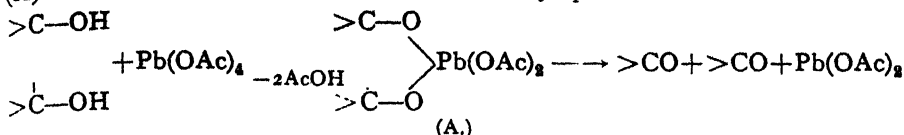


Ethylene glycol forms mono- and di-acetates, etc., some of the esters and ethers—*glycol mono-ethyl ether* and *glycol diacetate*—being employed as solvents for cellulose esters.

Two highly selective reagents, lead tetraacetate and periodic acid, readily effect fission of the carbon-carbon linkage in glycols when the hydroxyl groups are on contiguous carbon atoms.

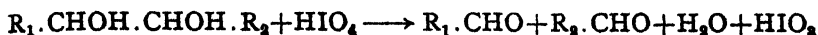
Lead tetraacetate (*Criegee's reagent*) is used chiefly in non-aqueous

solvents and probably functions by the formation of a lead intermediate (A) which then dissociates into two carbonyl products and lead acetate.



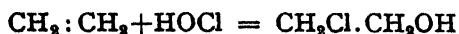
It is noteworthy that *cis*-glycols are oxidised in this way much more rapidly than the *trans*. Lead tetraacetate is thus an excellent reagent for structural and configurational diagnosis.

Periodic acid (Malaprade) reacts according to the following general equation.

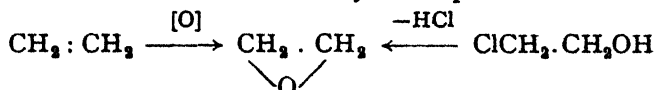


It also oxidises α -ketols ($-\text{CO}.\text{CHOH}-$), α -diketones ($-\text{CO}.\text{CO}-$), and α -ketonic aldehydes ($-\text{CO}.\text{CHO}$).

Ethylene chlorhydrin, $\text{CH}_2\text{Cl}.\text{CH}_2\text{OH}$, is manufactured by interaction of ethylene and chlorine water (hypochlorous acid).



It is a liquid miscible in all proportions with water. It is a valuable organic reagent. With alkali it gives ethylene oxide and this method is employed on the industrial scale. Another method for the preparation of this compound involves the oxidation of ethylene in presence of a silver catalyst.



Ethylene oxide boils at 10.7° , possesses an ethereal smell, and has a marked tendency to unite with a variety of substances, combination being accompanied by rupture of the ring; consequently it is frequently employed as a starting material for the preparation of other compounds.

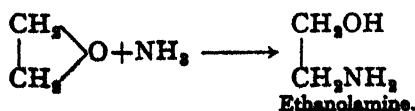
Dioxan, $\text{O} \begin{array}{c} \text{CH}_2.\text{CH}_2 \\ \text{CH}_2.\text{CH}_2 \end{array} \text{O}$, is used as a solvent, *e.g.* for cellulose

acetate. It melts at 9° , boils at 102° and is miscible in all proportions with water. One method of preparation is to heat glycol with concentrated sulphuric acid.

Amines derived from Dihydric Alcohols

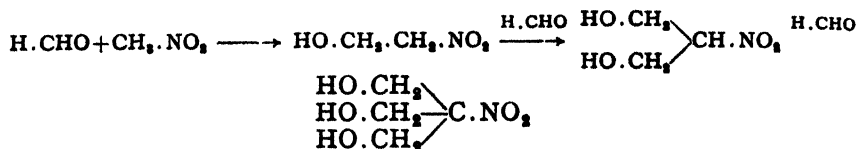
(a) ETHANOLAMINES¹

The simplest amino-alcohol, *ethanolamine*, is prepared by the action of ammonia on ethylene oxide or ethylene chlorhydrin.



¹ See C. B. Kremer, *J. Chem. Ed.*, 1942, 19, 80.

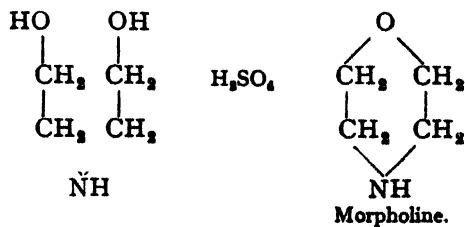
The process may be repeated, the products being *diethanolamine* $(\text{HOCH}_2\text{.CH}_2)_2\text{NH}$, and *triethanolamine* $(\text{HO.CH}_2\text{.CH}_2)_3\text{N}$. These and other amino-alcohols can also be obtained by the reduction of nitro-alcohols (Raney nickel and hydrogen), which are readily prepared by the condensation of nitro-compounds and aldehydes in presence of bases.



They have the properties both of alcohols and amines. Their basic properties have resulted in their use in industry as CO_2 absorbers. In recent years the amino-alcohols have been increasingly used in the manufacture of dyes, explosives, and medicinals. Perhaps their most useful property, however, is that they combine with the higher fatty acids to form soaps which cause no alkaline irritation and are powerful emulsifiers.

When, instead of ammonia, primary and secondary amines react with ethylene oxide hydroxy-alkyl bases (*hydramines*) and hydroxy-dialkyl bases (*alkamines*) are formed. Dimethylamine, for example, forms hydroxyethyl-dimethylamine, $\text{HO.CH}_2\text{.CH}_2\text{.N(CH}_3)_2$, which is of interest as being one of the fission products of the alkaloid morphine. Hydroxyethyl-diethylamine is used in the preparation of novocaine.

The amino-alcohols can be converted into the amino-ethers. For example, morpholine, is the inner anhydride of diethanolamine from which it is prepared by heating at 160° with 70 per cent. sulphuric acid.



It is strongly basic and boils at 128° .

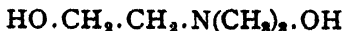
From aminoethyl alcohol it is possible to prepare aminoethyl ether, $\text{NH}_2\text{.CH}_2\text{.CH}_2\text{.O.C}_2\text{H}_5$, one of the simplest of the ether bases. Aminoethyl alcohol is heated to $150^\circ\text{--}160^\circ$ with concentrated hydrochloric acid, when it is converted into β -chloro-ethylamine hydrochloride; this on further treatment at $150^\circ\text{--}160^\circ$ with a solution of sodium ethylate yields the amino-ether.



Dimethylaminoethyl ether, $(\text{CH}_3)_2\text{N.CH}_2\text{.CH}_2\text{.O.C}_2\text{H}_5$, was isolated by Knorr as a disruption product of the alkaloids morphine, codeine, and

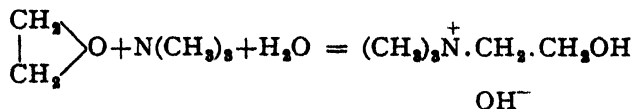
thebaine. It is formed by the interaction of dimethylamine and iodo-ether or from chloroethyl-dimethylamine and sodium ethoxide.

Choline, *hydroxyethyl-trimethyl-ammonium hydroxide*



is very widely distributed in plant and animal organisms, and is the most important basic constituent of lecithin.

The constitution of choline is shown by its hydrolytic products—a concentrated aqueous solution of the substance decomposes on boiling into trimethylamine and glycol—and also by its manner of formation. It may be obtained synthetically by heating trimethylamine with ethylene chlorohydrin, or by allowing trimethylamine and ethylene oxide to react in aqueous solution at ordinary temperature.



Choline is a non-crystallisable syrupy liquid, deliquescent in air and miscible in all proportions with water. It has a strong alkaline reaction and little physiological activity. On oxidation it is converted into betaIne (see p. 243).

Muscarine is the poisonous principle of the fungus *Amanita muscaria*, and is closely related to choline. Probably it is a basic hydroxy-aldehyde¹ of the formula $\text{C}_8\text{H}_{15} \cdot \text{CHOH} \cdot \text{CH}(\text{CHO}) \cdot \text{N}(\text{CH}_3)_3\text{OH}$

Neurine, *vinyl - trimethyl - ammonium hydroxide*, $\text{CH}_2 : \text{CH} \cdot \text{N}(\text{CH}_3)_3\text{OH}$, was discovered together with choline in 1865, by heating the brain of cattle with baryta-water. It is produced during the putrefaction of choline, or on boiling the latter with baryta-water. Neurine is also found among the ptomaines formed by the putrefaction of proteins, particularly in dead bodies. Unlike choline, to which it is so closely related in constitution, neurine is a powerful poison.

(b) ALKYLENE DIAMINES

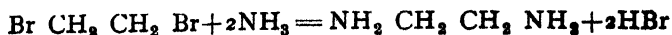
Alkylene diamines are an interesting series of compounds which may be derived from glycols by the replacement of both hydroxyl groups by amino groups.

They may be prepared synthetically by the methods used for alkyl amines (p. 175 *et seq.*), *e.g.* by the action of ammonia on alkylene bromides, or by the reduction of alkylene cyanides. Certain diamines are also formed during the putrefaction of flesh.

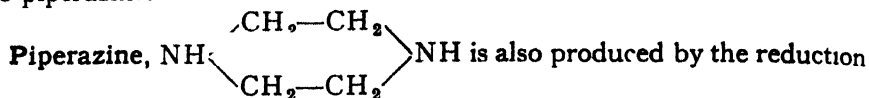
They are liquids or low melting solids of strong basic properties, which by loss of ammonia readily pass into cyclic imides.

¹ F. Kogl and H. Verdstra, *Ann.*, 1942, 552, 1.

Ethylene diamine, $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, may be obtained together with other products by heating ethylene dibromide to 100° with alcoholic ammonia.



When the hydrochloride of ethylene diamine is heated it is converted into piperazine.



of pyrazine. It is a strongly basic compound, m.p. 104° and b.p. 145° , which is soluble in water.

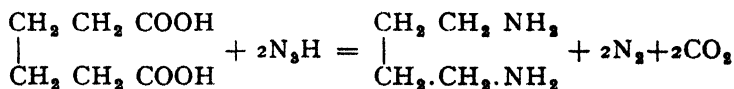
Tetramethylene diamine, *putrescine*, m.p. 27° ,



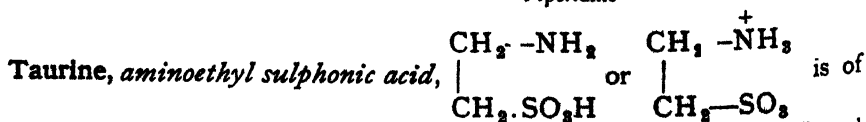
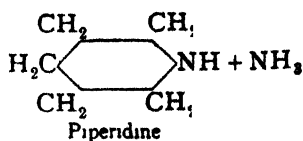
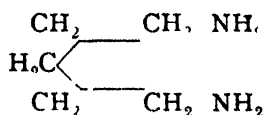
is formed by the putrefaction of flesh and of ornithine (see p. 246). It may be prepared by the reduction of ethylene cyanide.



A more recent method is to shake adipic acid, dissolved in concentrated sulphuric acid, with a solution of hydrazoic acid in chloroform (*Schmidt Reaction*)

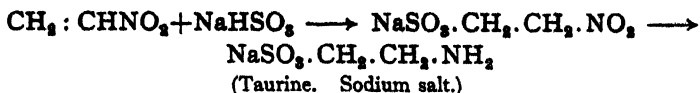


Pentamethylene diamine, *cadaverine*, $\text{NH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_2\text{NH}_2$, is of physiological interest, as it occurs among the products formed by the putrefaction of proteins and is therefore present in the body after death. It may be obtained synthetically by the reduction of trimethylene cyanide, $\text{CN}(\text{CH}_2)_3\text{CN}$. A more convenient method is to treat benzoyl-piperidine with phosphorus pentachloride and to replace the halogen atoms in the resulting 1:5-dichloropentane with amino groups, as indicated later. This process is reversed when pentamethylene diamine hydrochloride is heated, in which case ammonia is split off and piperidine or hexahydro-pyridine formed.

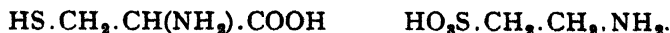


interest in connection with the above amino compounds. It is found combined with cholic acid as *taurocholic acid* in ox-gall (hence the name taurine) and in the gall of many other animals. Synthetically it is obtained

by the addition of sodium bisulphite to nitroethylene and subsequent reduction of the nitroethane sulphonic acid.



It is a crystalline compound which melts with decomposition at 240° . Nitrous acid converts it into *isethionic acid* (hydroxyethyl-sulphonic acid), $\text{CH}_2\text{OH} \cdot \text{CH}_2 \cdot \text{SO}_3\text{H}$ which is also formed by the action of fuming sulphuric acid on ethylene. In the animal organism taurine is formed from cysteine by oxidation and loss of carbon dioxide.



II.—TRIHYDRIC ALCOHOLS

These compounds contain three hydroxy groups attached to three different carbon atoms. Their chemical properties may be deduced from the presence of three primary or secondary alcoholic hydroxyl groups in the molecule, which can be brought into reaction individually or simultaneously to form ethers, esters and other derivatives.

Glycerol or *glycerine*, $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$, discovered in 1779 by Scheele, is prepared technically in large quantities by the hydrolysis (*saponification*) of animal fats or vegetable oils during the manufacture of soap and free fatty acids (p. 209). It is most easily obtained in the pure state when the saponification is effected by steam. The glycerol is purified by steam distillation, decolorised with animal charcoal, and finally concentrated under diminished pressure.

Recently a method has been devised for the manufacture of glycerol from propylene.

- (1) $\text{CH}_2 : \text{CH} \cdot \text{CH}_3 + \text{Cl}_2 \xrightarrow{500^\circ} \text{CH}_2 : \text{CH} \cdot \text{CH}_2\text{Cl} + \text{HCl}$
Allyl chloride
- (2) $\text{CH}_2 : \text{CH} \cdot \text{CH}_2\text{Cl} + \text{NaOH} \longrightarrow \text{CH}_2 : \text{CH} \cdot \text{CH}_2\text{OH} + \text{NaCl}$
Allyl alcohol
- (3) $\text{CH}_2 : \text{CH} \cdot \text{CH}_2\text{OH} + \text{HOCl} \longrightarrow \text{CH}_2\text{OH} \cdot \text{CHCl} \cdot \text{CH}_2\text{OH}$
- (4) $\text{CH}_2\text{OH} \cdot \text{CHCl} \cdot \text{CH}_2\text{OH} + \text{NaOH} \longrightarrow \text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH} + \text{NaCl}$

The most interesting stage is the first—the “*hot chlorination*” at 500° —in which substitution and not addition occurs and allyl chloride results. The yields are excellent (80-95 per cent. at each stage).

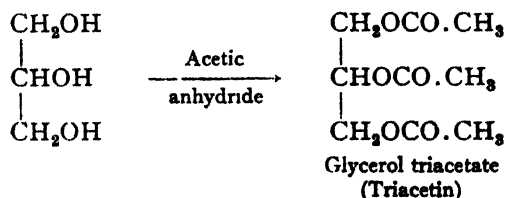
Allyl chloride, allyl alcohol, and glycerol are manufactured by this method.

Glycerol can also be prepared technically by a fermentation process and advantage is taken of this in war-time when other sources are not available. Germany, for example, in the first world war was able to manufacture more than one million kilogrammes of glycerol per month

by this process. The method is based on the observation that the proportions of products formed during the fermentation of sugar are greatly influenced by the presence of substances which are somewhat alkaline. Disodium sulphite proved to be particularly efficient and with increasing quantities of this salt the fermentation of sugar is so influenced that the formation of ethanol and carbon dioxide diminishes while that of glycerol and acetaldehyde increases.

Pure glycerol, b.p. 290° , is a colourless viscous syrup of sweet taste (from which it derives its name). At 0° it gradually solidifies to crystals, m.p. 17° . It is miscible in all proportions with water and alcohol, but is insoluble in ether.

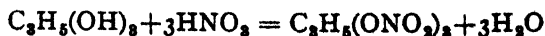
Glycerol behaves both as a primary and as a secondary alcohol as shown by mild oxidation to glyceraldehyde, $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHO}$ and dihydroxyacetone, $\text{CH}_2\text{OH}.\text{CO}.\text{CH}_2\text{OH}$. Stronger oxidation with nitric acid gives glyceric acid, $\text{CH}_2\text{OH}.\text{CHOH}.\text{COOH}$. The presence of three hydroxyl groups in the molecule is established by acetylation with acetic anhydride to give glycerol triacetate (triacetin).



The constitution of glycerol has been confirmed by a number of syntheses including the reduction of dihydroxyacetone.

Glycerol is used extensively for the manufacture of nitroglycerine and as a plasticiser, and in the manufacture of alkyd resins. A small proportion is utilised in the preservation of such articles of food as require to be kept moist (fruits, etc.). Other uses to which it is put include the manufacture of cosmetics and skin preparations, colour printing and the production of shoe blacking.

Nitroglycerine, *glyceryl trinitrate*, $\text{C}_3\text{H}_5(\text{O}.\text{NO}_2)_3$, is obtained by treating glycerol with a mixture of nitric and sulphuric acids.



The name nitroglycerine is misleading, as the compound it describes is not a nitro-compound but an ester of nitric acid, which is hydrolysed with alkalis in the normal manner to give glycerol and a metallic nitrate.

In the pure state nitroglycerine is a heavy, colourless oil of sp. gr. 1.6. It has a sweet taste and is poisonous, its vapour producing headache, vertigo and loss of consciousness. It crystallises in two forms: labile rhombic plates, m.p. 2° and prismatic needles, m.p. 13.2° .

Nitroglycerine burns quietly if ignited in small quantities, but explodes

violently when rapidly heated, or on being struck or detonated with mercury fulminate. The decomposition proceeds according to the equation



In the pure state the compound is not adapted for general use as an explosive, owing to its fluid nature and extreme sensitiveness to mechanical shock. Further, the shattering rapidity with which the explosion is completed renders it useless as a propellant for artillery. In 1867 the Swedish chemist, Alfred Nobel, first showed how nitroglycerine could, by admixture with other substances, be handled and used with safety. When the liquid is mixed with about one-third of its weight of kieselguhr—a fine siliceous earth—it forms a plastic mass of the consistency of putty, known as **dynamite**, from which charges of definite weight are readily made. In this case the kieselguhr functions merely as an indifferent medium of dilution. Apparently the particles of nitroglycerine are separated from one another by the very finely divided kieselguhr, thus slowing down the speed of decomposition and allowing the effect of explosion to be calculated. Further, under ordinary conditions dynamite is not liable to be exploded accidentally. In some countries, notably America, wood pulp or wood powder is substituted for kieselguhr. Dynamite is employed in blasting but not as a propellant for projectiles, since the walls of the gun are not capable of withstanding the sudden impulse. For mining purposes in Great Britain dynamite has very largely been displaced by other mixtures, such as *blasting gelatine* (nitroglycerine with 7 to 10 per cent. of collodion cotton), and *gelignite* or *gelatine dynamite*.

In the year 1889 Nobel succeeded in adapting nitroglycerine for use as a *smokeless propellant powder* by mixing it with nitrocellulose (p. 343). According to Nobel's process, equal parts by weight of these two substances are intimately incorporated with one another, and while the mass is still plastic it is formed into cubes, rods or other regular shapes. In the product so obtained the components exist in the form of a solid solution, and as a result of the horny consistency of the material it decomposes comparatively slowly on ignition. The best known nitroglycerine powder is *cordite*, composed of 65 per cent. nitrocellulose, 30 per cent. nitroglycerine and 5 per cent. vaseline.

Nitroglycerine is also utilised to a small extent in medicine for asthma, and in cases of poisoning by carbon monoxide or coal gas.

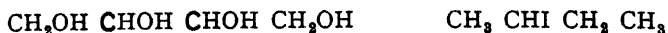
A concise and interesting account of the history and uses of explosives is given by Read in *Explosives* (Pelican Books).

III.—HIGHER POLYHYDRIC ALCOHOLS¹

A representative of the tetrahydric alcohols has long been known in **erythritol**, $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CH}_2\text{OH}$, which occurs in the

¹ These contain asymmetric atoms, which are indicated in the formulae by heavier type.

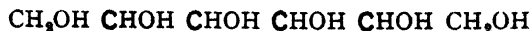
free state in nature and in the form of *erythrin* (the erythritol ester of orsellinic acid) in many lichens and algæ. The natural product is the inactive modification, identical with that obtained by the reduction of D-erythrose. Erythritol forms large clear crystals of m.p. 120° and has a very sweet taste. It dissolves readily in water, only with difficulty in ordinary alcohol, and not at all in ether. Its constitution as a normal straight chain derivative follows from its conversion into *n*-secondary butyl iodide on reduction with hydriodic acid.



Nitric acid converts it into the nitric ester, $\text{C}_4\text{H}_8(\text{ONO}_2)_4$, also known as *nitro-erythritol*, which like nitroglycerine is a powerful explosive. On oxidation it yields first *erythrose*, a mixture of the mono-aldehyde, $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CHO}$, and the ketone $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CO} \cdot \text{CH}_2\text{OH}$ and finally *erythronic acid* (trihydroxybutyric acid), $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{COOH}$.

Among the **pentahydric alcohols** or pentitols the best known representatives are **arabitol**, **xylitol** and **adonitol**. These all possess the constitutional formula $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$, containing two asymmetric carbon atoms, and are stereoisomeric with one another. A homologue of this series is **rhamnitol**, $\text{CH}_3 \cdot (\text{CHOH})_4 \cdot \text{CH}_2\text{OH}$, which is formed by the reduction of rhamnose.

Hexitols, or **hexahydric alcohols**, are of importance not only because they occur extensively in nature, but also on account of their close relationship to the simple class of sugars known as hexoses. The latter are aldehydes or ketones corresponding to the hexahydric alcohols, into which they may be converted by reduction with sodium amalgam. Considering their similarity in structure, it is not surprising to find that the hexitols and the hexoses possess many properties in common, such as sweet taste and solubility in water. Three alcohols of this class may be mentioned, **mannitol**, **dulcitol** and **sorbitol**, which are all stereoisomerides of the formula



Ordinary or D-**mannitol** occurs widely distributed in the vegetable kingdom, being found especially in manna, the evaporated sap of the manna tree. It is obtained commercially by the electrolytic reduction of D-mannose. D-Mannitol crystallises in needles or prisms melting at 166° .

Dulcitol, m.p. 188° , is optically inactive and occurs chiefly in dulcite manna, from which it is prepared. It is also formed by the reduction of lactose and of D-galactose.

D-**Sorbitol**, $\text{C}_6\text{H}_{14}\text{O}_6 + \text{H}_2\text{O}$, is present in the berry of the mountain ash. It is prepared industrially by the high-pressure catalytic reduction of corn sugar (dextrose).

XIII

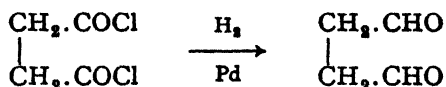
Dialdehydes and Diketones

These interesting compounds are valuable starting-points for the synthesis of various cyclic derivatives. They may be prepared by the catalytic reduction of the corresponding acid chlorides¹ with hydrogen in the presence of finely divided palladium. Only two of the **dialdehydes**, namely glyoxal and succindialdehyde, will be dealt with here.

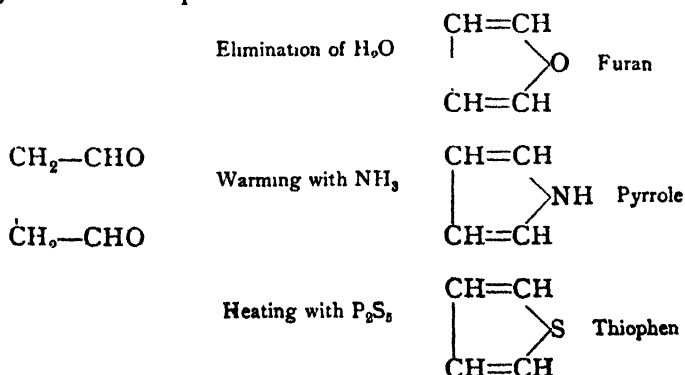
Glyoxal, CHO·CHO, is prepared in the laboratory by the oxidation of acetaldehyde by selenium dioxide. Like other aliphatic dialdehydes, it polymerises very readily and in fact is generally obtained in the monomolecular form by distillation of **poly-glyoxal**.

As would be expected, glyoxal possesses a strong aldehydic character. It combines, for example, with two molecules of sodium bisulphite to give a crystalline compound, by means of which it is usually isolated.

Succindialdehyde, CHO·CH₂·CH₂·CHO, is formed when succindialdioxime—obtained by the interaction of pyrrole and hydroxylamine—is treated in aqueous suspension with nitrous acid. It is more readily prepared, however, by reduction of the acid chloride of succinic acid with hydrogen and a palladium catalyst in boiling xylene.



By means of succindialdehyde it is possible to pass in a simple manner from an aliphatic compound to the three typical heterocyclic compounds furan, pyrrole and thiophen.



For an example of its use in synthesising still more complex heterocyclic compounds, see *tropinone*.

DIKETONES

Nomenclature.—According to the relative positions of the >CO groups, these compounds are distinguished as α- or 1 : 2-diketones containing the group CO·CO ; β- or 1 : 3-diketones containing the group

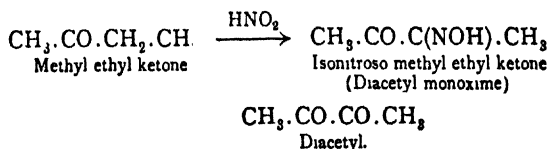
¹ K. W. Rosenmund and co-workers, *Ber.*, 1921, 54, 2888 ; 1922, 55, 609.

$\text{CO} \cdot \text{CH}_3 \cdot \text{CO}$; γ - or 1:4-diketones containing the group $\text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}$, and so on. In some cases names are also in common use which represent α -ketones as formed by the union of two acid radicals $\text{R} \cdot \text{CO}-$, and β -ketones as acyl-substituted ketones, *e.g.* diacetyl, $\text{CH}_3 \cdot \text{CO} \cdot \text{CO} \cdot \text{CH}_3$, and acetyl-acetone, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_3$.

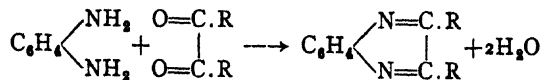
According to the Geneva nomenclature, the diketones are named after the corresponding hydrocarbon by adding the termination -dione, *e.g.* acetyl-acetone or 2:4-pentane-dione.

1. α - or 1:2-Diketones

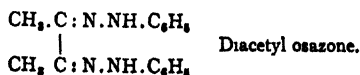
The α -diketones are yellow, volatile liquids of pungent smell, which are obtained from their monoximes, the isonitroso-ketones, by boiling with dilute sulphuric acid. *Isonitroso-ketones* are prepared by the action of nitrous acid on ketones.



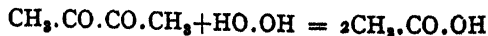
α -Diketones condense with *o*-phenylene diamines to form cyclic compounds known as *quinoxalines*.



With hydroxylamine the α -diketones yield monoximes (isonitroso-ketones) as well as dioximes (*glyoximes*). Phenylhydrazine forms monohydrazones and dihydrazones, the latter also being known as *osazones*, *e.g.*,



Diacetyl, $\text{CH}_3 \cdot \text{CO} \cdot \text{CO} \cdot \text{CH}_3$, is obtained by the method described above, and is prepared industrially by treating vinylacetylene with a solution of mercuric sulphate in sulphuric acid and heating the resultant compound with hydrochloric acid. It is a yellow liquid of penetrating smell and b.p. 88° , the vapour of which possesses the colour of chlorine. With hydrogen peroxide it is readily decomposed into two molecules of acetic acid.

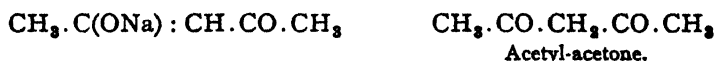
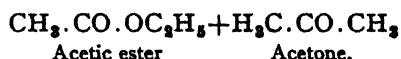


Diacetyl dioxime, dimethyl glyoxime, $\text{CH}_3 \cdot \text{C}(\text{NOH}) \cdot \text{C}(\text{NOH}) \cdot \text{CH}_3$, is conveniently prepared by the action of hydroxylamine on the monoxime, formed as described above from methyl ethyl ketone and nitrous acid. It gives a dark red precipitate with solutions of nickel salts, and is used for the qualitative and quantitative determination of this metal.

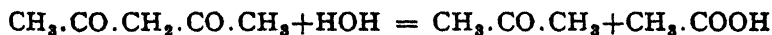
2. β - or 1 : 3-Diketones

Preparation.— β -Diketones are usually obtained by the condensation of esters with ketones, a reaction of general application discovered by Claisen. It should be noted that esters can also be condensed with esters, in which case β -ketonic esters of the general formula $R.CO.CH_2.COOR$ are obtained. This reaction, known as the *Claisen condensation*, involves the elimination of alcohol between the group $R.COOC_2H_5$ of an ester and the $CH_3.CO-$ of a ketone (or the $R.CH_2.CO-$ of a second ester molecule), and may be effected by means of the following reagents : 1. an alcoholic solution of sodium ethoxide ; 2. alcohol-free sodium ethoxide ; 3. metallic sodium ; or 4. sodamide. The classical prototype of this condensation is the conversion of ethyl acetate into aceto-acetic ester, and the course of the reaction will be discussed under this substance.

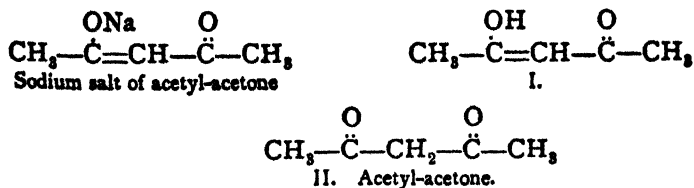
Acetyl-acetone, $CH_3.CO.CH_2.CO.CH_3$, is prepared by condensing acetic ester with acetone in the presence of one of the above agents, *e.g.* metallic sodium. The sodium salt of acetyl-acetone so obtained is then converted into the insoluble copper salt, from which the free ketone is liberated by treatment with dilute sulphuric acid.



It is a colourless, pleasant-smelling liquid, b.p. 137° . When boiled with water it decomposes into acetone and acetic acid.



Constitution and Properties of the β -Diketones.—The β -diketones possess an acidic character as shown by the formation of metallic derivatives, many of which are insoluble in water but soluble in benzene, chloroform and other organic solvents. Characteristic copper salts are also formed which are only sparingly soluble in water. In general it is assumed that the metal is united to oxygen, *i.e.*, that the salts are derived from the acidic or enol form I., while the free ketones may represent equilibrium

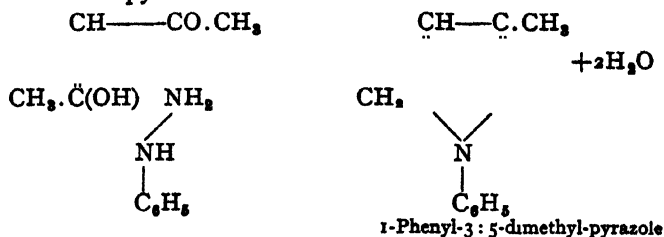


mixtures of the keto and enol forms (*cf.* p. 277), although they are usually written as diketo-compounds II.

The *enol form of acetyl-acetone* I. has been isolated in the pure state by crystallising the equilibrium mixture from petroleum ether at a low

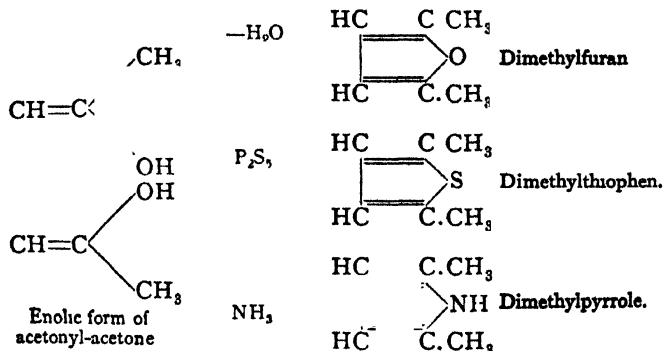
temperature.¹ A more convenient method of preparation is to distil the mixture from a glass flask,² when the traces of alkali from the glass catalytically convert the greater part of the keto into the enol form. The distillate contains about 99 per cent. enol form.

Among the great number of condensations undergone by β -diketones, one deserving special mention is their reaction with hydrazines to give *pyrazole derivatives*. This reaction is the most useful of all methods for the preparation of pyrazoles.



3. γ - or 1:4-Diketones

A compound of this type is **acetonyl-acetone**, 2:5-*hexane-dione*, $\text{CH}_3 \text{CO} \text{CH}_2 \text{CH}_2 \text{CO} \cdot \text{CH}_3$, which is conveniently prepared from β -diaceto-succinic ester by boiling with sodium hydroxide. It is a clear, pleasant-smelling liquid, b.p. 191° under 750 mm., which dissolves readily in water, alcohol and ether.



The γ -diketones are readily converted into derivatives of furan, thiophen and pyrrole (see above formulæ).

XIV

Monobasic Aldehydic and Ketonic Acids

These acids may be regarded as oxidation products of the hydroxy-acids (see p. 252). In the ease with which they are converted into cyclic derivatives, however, and in the frequent occurrence of isomerism, they

¹ L. Knorr and H. Fischer, *Ber.*, 1911, 44, 2771. ² K. H. Meyer and Hopff, *Ber.*, 1921, 54, 579

show many resemblances to dialdehydes and diketones, and it is more convenient to discuss them at this stage. As might be expected, these acids possess the dual character of carboxylic acids and of aldehydes or ketones.

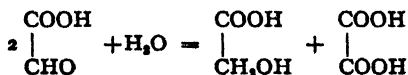
Glyoxalic acid, $\text{CHO} \cdot \text{COOH}$, H_2O , is the best known aldehydic acid. It occurs in young plants and unripe fruit (*e.g.* gooseberries and currants), and can be formed by the oxidation of ethyl alcohol with HNO_3 or in good yield by the electrolytic reduction of oxalic acid in sulphuric acid solution. It may be obtained synthetically from dichloroacetic acid by heating with water, a reaction which establishes its structure.



The molecule of water is firmly held in the molecule which is sometimes regarded as dihydroxyacetic acid $(\text{HO})_2\text{CH} \cdot \text{COOH}$. The anhydrous acid is obtained by evaporation of the aqueous solutions of the acid *in vacuo* over phosphorus pentoxide.

Glyoxalic acid gives the usual reaction of aldehydes, reducing ammoniacal silver solutions, combining with sodium bisulphite, and forming an oxime. It also gives the reactions of a carboxylic acid.

When boiled with alkalis it yields glycollic acid and oxalic acid.



Ketonic acids are of more importance than aldehydic acids. Like the diketones (p. 269) they are distinguished as α -, β -, γ - or δ -keto-acids according to the position of the $>\text{CO}$ group with regard to the carboxyl.

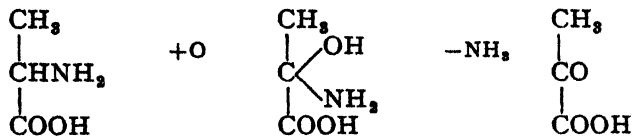
$\text{CH}_3 \cdot \text{CO} \cdot \text{CO}_2\text{H}$
 α -Keto-propionic acid,
Acetyl-formic acid.

$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$
 β -Keto-butyric acid,
Acetoacetic acid.

$\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$
 γ -Keto-valeric acid.
 β -Acetyl-propionic acid.

The α - and γ -keto-acids are stable even in the free state, but the free β -keto-acids readily undergo decomposition.

In the protein metabolism of the living organism α -ketonic acids are formed by the oxidative deamination of α -amino-acids. This is the commonest method by which amino-acids are decomposed in the animal body. It is assumed that an α -hydroxy- α -amino-acid occurs as an intermediate.



Pyruvic acid, **pyro-racemic acid**, $\text{CH}_3 \cdot \text{CO} \cdot \text{COOH}$, is the simplest α -keto-acid, and is prepared by distilling tartaric acid with potassium hydrogen sulphate (hence the name). It may be synthesised by the hydrolysis of acetyl cyanide.

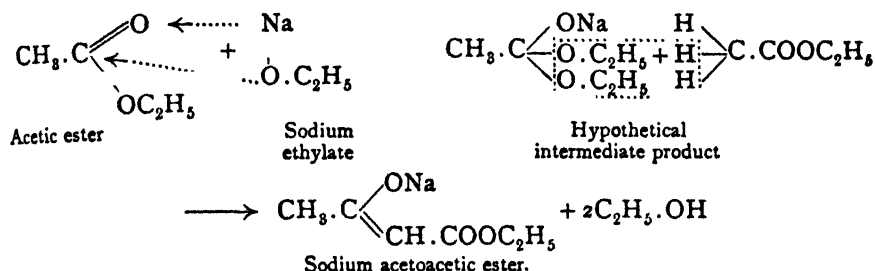


α -Ketonic acids, in general, are prepared by hydrolysing acyl nitriles obtained by treating acid chlorides with silver or copper cyanide. This method of preparation confirms their constitution.

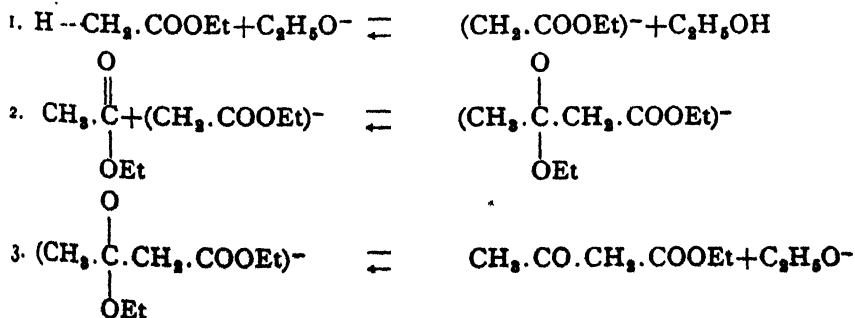
give ethyl acetoacetate is the classic example of the *Claisen condensation*—a term that is now used to include other condensations, such as ketone-ester and aldehyde-ester condensations, effected by bases.

The mechanism of acetoacetic ester formation has been and is still a matter of controversy. Claisen, in 1887, advanced the view that the formation of sodium acetoacetic ester is not induced primarily by the action of sodium, but by sodium ethoxide produced from alcohol contained as an impurity in the ethyl acetate employed. This is in agreement with the observation that, when the ethyl acetate is carefully freed from alcohol, the reaction with sodium at first is very slow, but increases as ethyl alcohol is formed according to the equation given above.

Claisen's theory of the acetoacetic ester reaction is expressed in the following scheme :—

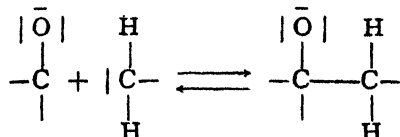


Claisen's scheme, however, is not without its weaknesses. It does not account for the formation of β -keto-esters from esters such as ethyl isobutyrate, nor does it give expression to the general nature of the reaction in which other bases such as triphenylmethyl-sodium or Grignard reagents such as mesitylmagnesium bromide replace sodium ethoxide. It is, indeed, hard to avoid the conclusion that the reaction involves an ionic mechanism—a revival of earlier suggestions made by Lapworth and others.¹ The essentials of the modern theory are given in the following scheme in which the base (*e.g.* ethoxide ion) removes a proton from a molecule of ester to form a *carbanion*, which then adds on to the carbonyl group of a second ester molecule.



¹ H. B. Watson, *Ann. Reports*, 1939, 36, 210. C. R. Hauser and B. E. Hudson in *Organic Reactions* (ed. by Roger Adams), 1, 266. Arndt and Eistert, *Ber.*, 1936, 69, 2381.

In the second stage the ester probably reacts in the polar form in which the oxygen is relatively negative and the carbon positive. A crude representation of the reaction is the following, in which each dash represents a pair of electrons :—



The above mechanism accounts very satisfactorily for the formation of ethyl isobutyrylisobutyrate from ethyl isobutyrate in the presence of triphenylmethyl ion, the stronger base, sodium triphenylmethide, effecting condensation where the weaker base, sodium ethoxide, fails.

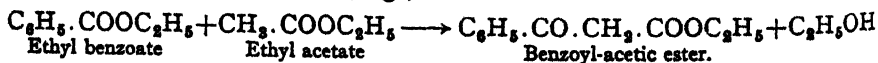
Further evidence for this is provided by the racemisation of certain optically active esters in contact with sodium ethoxide,¹ thus demonstrating the existence of the equilibrium represented by stage 1 in the above equations.



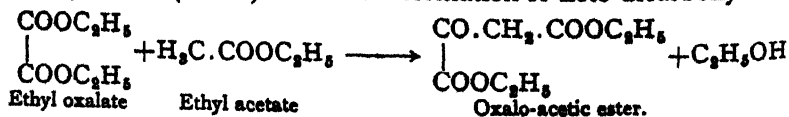
The racemisation observed is due to the symmetry of the anion formed, and is not explained by simple addition of the sodium ethoxide to the ester (first stage of the Claisen mechanism).

The Claisen condensation affords a simple example of the activating influence of unsaturated groups (COOH, COOEt, C=O, C₆H₅, etc.) which render the hydrogen atoms on contiguous carbon atoms mobile and reactive. Great use is made of this in synthetic work and the acetoacetic ester condensation is the prototype of a large number of similar reactions, some of which have already been described on p. 271. These condensations are of great value in synthetic chemistry, and may be further illustrated by the following examples taken from the investigations of Claisen and Wislicenus.

When sodium ethoxide is allowed to interact with a mixture of two esters of monobasic acids, a ketonic ester of constitution similar to that of acetoacetic ester is formed, *e.g.*,



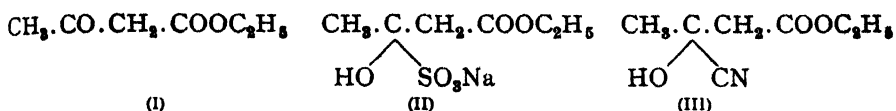
The use of a mixture of ethyl acetate (1 mol.) and an ester of a dicarboxylic acid (1 mol.) leads to the formation of keto-dicarboxylic esters:



¹ Kenyon and Young, *J.*, 1940, 216.

Tautomerism of Acetoacetic Ester.—Acetoacetic ester affords the oldest and probably the most important example of tautomerism. Over a long period of years it has been carefully and exhaustively investigated by many workers including Knorr and Kurt Meyer. From the first its constitution attracted attention and gave rise to controversy. Geuther assigned to it an *enolic* formula (see below) whereas Frankland and Duppa regarded it as a ketonic compound. Detailed researches showed indeed that both formulæ are required to describe adequately all the chemical properties of the ester and we now know that the ester is an equilibrium mixture of the enolic and ketonic forms.

Ethyl acetoacetate reacts as a saturated β -keto ester (I). It forms a bisulphite compound (II) and a hydrogen cyanide derivative (III). The presence of the ketonic group is

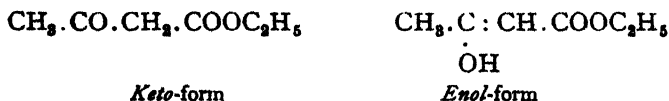


confirmed by other reagents such as hydroxylamine, phenylhydrazine, etc. The presence of the contiguous methylene group is established by the formation of the dialkyl derivative mentioned on p. 281.

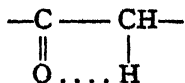
The ester also reacts as ethyl β -hydroxycrotonate (IV). It is immediately attacked by bromine (see below), and with diazomethane forms the O-methyl ether, β -methoxycrotonic ester (V).



These and other reactions (p. 279) provide convincing evidence that acetoacetic ester reacts both in the *keto*-form and in the *enol*-form and it has long been accepted that the ester is an equilibrium mixture of these two forms.



The two forms are structural isomers differing mainly in the position of a hydrogen atom, which in the keto form is attached to the carbon atom of the methylene group and in the enol is attached to the oxygen atom



of the carbonyl group. Such a change in position is easily envisaged since the hydrogen atom (or more correctly the proton) can migrate readily to the nearby oxygen atom. The ester accordingly is a tautomeric or more particularly a *prototropic* substance.

That acetoacetic ester is indeed a mixture of tautomers in equilibrium was first shown conclusively by Knorr and his co-workers. From the results of his investigations on the tautomerism of other substances Knorr concluded that the velocity of isomerisation of the two forms of acetoacetic ester should not be very high and that a separation might be effected at low temperatures. This he confirmed experimentally by cooling the ester to the temperature of ether and solid carbon dioxide (-78°) and showing that at this temperature the interconversion of the two forms is almost completely arrested, thereby enabling the isomerides to be isolated without any great difficulty.

The Keto Form.—The keto form, $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOC}_2\text{H}_5$, is obtained from the ordinary ester by freezing it out at -78° . At this temperature it crystallises from its solutions in alcohol, etc., and may thus be separated by filtration. The keto-ester is reasonably stable and at low temperatures may be preserved for a very long time without noticeable change. Even at room temperature, in the absence of catalysts, it returns only slowly to the equilibrium mixture during the course of weeks or months.

The keto form differs comparatively little from the ordinary (equilibrium) ester, as may be seen from the following data :

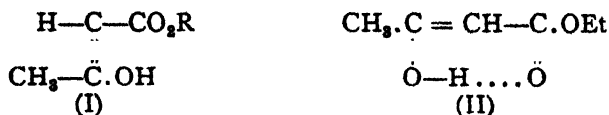
	<i>Keto-ester</i>	<i>Equilibrium Mixture</i>
Boiling-point (2 mm.)	40° to 41°	$39\text{--}40^\circ$
Melting-point	-39° (sharply)	-45° to -43° (not sharply)
Refrac. index, n_D^{20}	1.4225	1.4480

The inference from this data that ordinary acetoacetic ester is mainly the keto-form is clear (see below). Physical and chemical methods show that the ester contains 93 per cent. of the keto form and 7 per cent. of the enol.

The Enol Form.—*cis-Hydroxy-crotonic ester*, $\text{CH}_3\cdot\text{C}(\text{OH})\text{:CH}\cdot\text{COOC}_2\text{H}_5$ was obtained by Knorr by treating the sodium compound of acetoacetic ester in ether with dry hydrogen chloride at -78° . A simpler method was devised by Kurt Meyer and is based on two factors : the greater volatility of the enolic form and the small effect of quartz compared to glass in catalysing the interconversion of the two tautomeric forms. By distilling acetoacetic ester in a quartz apparatus it is therefore possible to distil off the small amount of enol present. A useful variant of this is to distil the equilibrium mixture from a glass flask into a quartz receiver. As the enol distils off, more enol is formed in the equilibrium mixture by the catalytic effect of the glass and eventually the equilibrium mixture is completely converted into this form.

The lower boiling-point of the enol noted above is at first sight surprising since enolic substances generally have higher boiling-points than the corresponding carbonyl compounds due to their intermolecular association. The enol, however, has the *cis*-configuration (I) which permits the

formation of an *intramolecular* hydrogen bond between the two oxygen atoms (II). In consequence no hydroxyl group is available for *inter-*



molecular hydrogen bond formation. Molecular association is thereby diminished and the substance boils at a lower temperature than the keto form.

A striking property of acetoacetic ester, which first led to the assumption of an enolic form, is its capacity to form salts. Treatment with alkali yields salts which can be isolated in the crystalline state. The ester therefore behaves as a weak acid and this is not explained by the keto formula. On the other hand the enolic form with a carbon atom attached both to a hydroxy group and a double bond closely resembles the carboxyl group. Hence it is easy to account for the acidic properties



of the ester. The presence of the enol grouping is confirmed by the characteristic ferric chloride coloration given by the ester. Such colorations are given only by compounds such as phenols which contain the $\text{C}(\text{OH})=$ grouping.

There has been much discussion on the constitution of the salts and two formulæ (I and II) have been proposed.



The problem, however, is resolved if we consider the acetoacetic ester anion. This will exist in two forms (III and IV) derived from the salts I and II. Forms III and IV are clearly resonating structures.



The product obtained from a given reagent may therefore be expected to occur either at the oxygen atom or at the α -carbon atom and will depend partly at least on the nature of the reagent. This is found to be so in practice. Acetyl chloride, for instance, gives predominately the O-acetyl derivative (V) and a very small quantity of the C-acetyl product (VI).



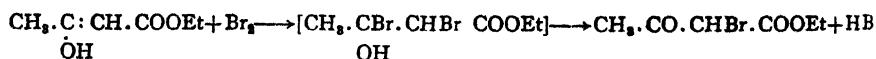
Methyl iodide on the other hand gives only the C-methyl compound.

The isomerisation velocity of the tautomeric forms of acetoacetic ester is considerably increased by catalysts. Contact with soft alkali glass, a little vapour of hydrochloric acid, tripropylamine, cigarette smoke, or merely handling the liquid in the impure air of a laboratory is sufficient in a few seconds or minutes to convert the enolic form in the equilibrium mixture.

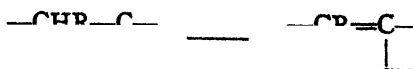
The Equilibrium Mixture.—As already stated, under ordinary conditions the ester is a mixture containing about 7 per cent. of the enol form. The position of equilibrium, however, is greatly influenced by number of factors such as temperature, solvent, etc. The solvent effect is shown in the following table.

<i>Solvent</i>	<i>Per cent En</i>
Water .	0.4
Methanol .	6.9
Nitrobenzene .	10.1
Benzene .	16.2
Hexane .	46.4
Vapour .	— — —

The enol content can be determined either by physical or chemical methods. When the latter are used it is essential that the reagents should react rapidly, since the keto-enol interchange rate is greatly influenced by the presence of hydrogen or hydroxyl ions. The method most commonly used is that of Kurt Meyer, which is based on the rapid absorption of bromine by the enol form in contrast to the non-reactivity of the keto form. The determination is effected by titrating the ester with a standard solution of bromine, the end point being reached when the colour of bromine persists.



Related to keto-enol tautomerism is *thiono-thiol tautomerism* which is observed in analogous sulphur compounds



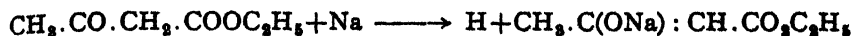
Acetoacetic Ester and its Synthetic Reactions

Acetoacetic ester is a colourless, pleasant-smelling liquid, b.p. 181°, which is sparingly soluble in water and gives a deep violet coloration with ferric chloride.

Owing to its great reactivity it is to be classed as one of the most important organic compounds, from which a large number of other substances may be prepared. The utility of acetoacetic ester as a synthetic

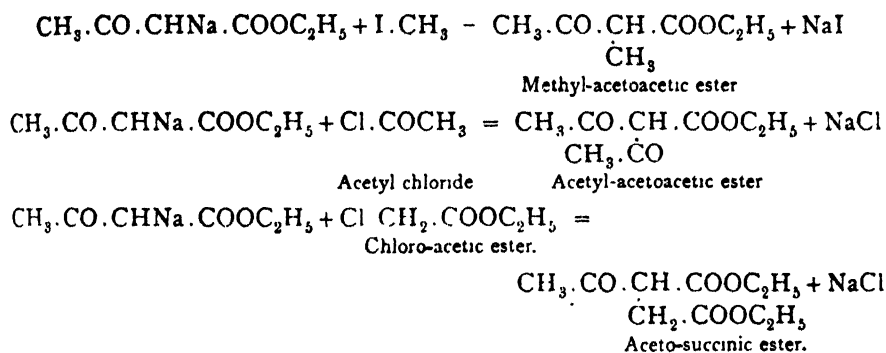
¹ A. Schonberg and W. Acker *J.* 1945 108.

reagent depends partly on the ease with which two of the hydrogen atoms may be replaced by sodium. When allowed to interact with metallic sodium an evolution of hydrogen occurs with the simultaneous formation of a sodium salt :

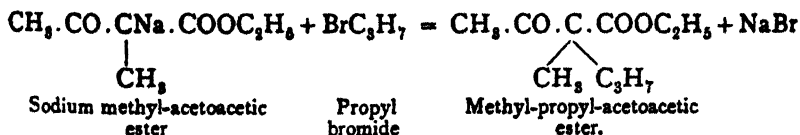


The sodium salt is more conveniently prepared by treating the ester with an alcoholic solution of sodium ethoxide.

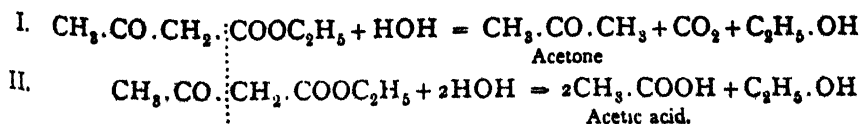
By making use of this sodium compound a variety of groups can be introduced into the acetoacetic ester molecule. On bringing it into reaction with an organic halogen compound a separation of sodium halide takes place and the two organic radicals unite together. In the following examples the sodium derivative is written as $\text{CH}_3 \cdot \text{CO} \cdot \text{CHNa} \cdot \text{COOC}_2\text{H}_5$, in order to abbreviate and simplify the equations—although the constitution of the metallic compound is probably more accurately expressed by resonance formulae (p. 279).



These mono-substituted esters also react with sodium ethoxide to give sodium derivatives, which by interaction with an organic halogen compound yield disubstituted acetoacetic esters, *e.g.*,

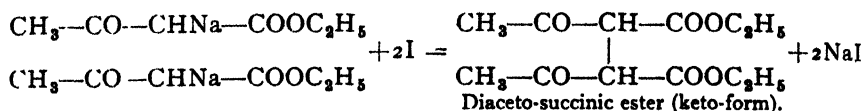


The great synthetic value of acetoacetic ester lies less in the production of the above types of compounds than in the simpler substances to which they give rise on hydrolysis. Acetoacetic ester may be hydrolysed in two ways, which are distinguished according to the nature of the product as "**ketonic hydrolysis**" (I) and "**acid hydrolysis**" (II) respectively.



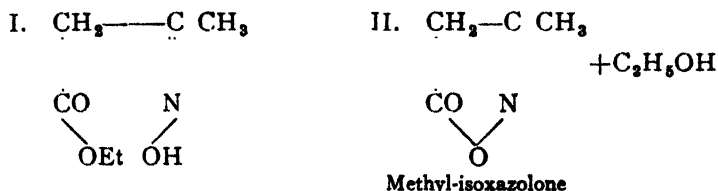
Ketonic hydrolysis occurs chiefly on treatment with hot dilute acids¹ or alkalis, or by heating with water in a closed tube to 200°, whereas acid hydrolysis is brought about by heating with concentrated alkalis. Since the above-mentioned derivatives of the ester can also be hydrolysed in a similar manner to yield ketones or acids, we have here a *general method for the preparation of mono- and di-substituted methyl ketones* of the type of $R.CH_2.CO.CH_3$ and $RR'CH.CO.CH_3$, and of *mono- and di-substituted acetic acids* $R.CH_2.COOH$ and $RR'CH.COOH$.

Two molecules of acetoacetic ester may be coupled up with one another by the action of iodine on sodium acetoacetic ester. The interesting substance *diaceto-succinic ester*, which is formed, has been isolated in several tautomers, the study of which was of considerable theoretical value. On ketonic hydrolysis it yields acetonyl-acetone (p. 272).

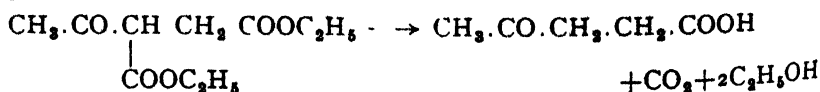


Finally, it should be noted that *acetoacetic ester unites with certain nitrogen compounds* such as ammonia, amines, hydrazines and hydroxylamine. These reactions are of great importance for the synthesis of a variety of heterocyclic compounds, as may be seen from the following example.

Hydroxylamine interacts with acetoacetic ester to form the oxime (I), which is readily transformed into *methyl isoxazolone* (II).



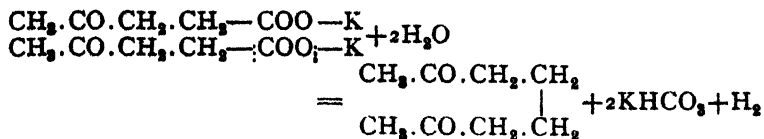
Laevulinic acid, $CH_3.CO.CH_2.CH_2.COOH$, m.p. 32.5°, is the simplest γ -ketonic acid. It is formed when a hexose, especially laevulose, is boiled with dilute sulphuric or hydrochloric acid. Laevulinic acid is prepared by heating starch or cane sugar with hydrochloric acid. It may be obtained synthetically by combining sodium acetoacetic ester with chloro-acetic ester and submitting the resulting product to ketonic hydrolysis:



The acid is crystalline; it is very readily soluble in water, alcohol, and ether; shows the characteristic reactions of ketones (formation of

¹ According to Dehn and Jackson, *J.A.C.S.*, 1933, 55, 4284, very high yields of ketones may be obtained by use of phosphoric acid.

oxime, hydrazone, etc.); and on electrolysis of its potassium salt yields 2:7-octanedione.

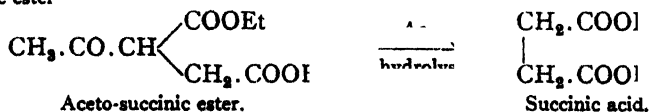


XV

Polybasic Acids

I.—SATURATED DIBASIC ACIDS, $\text{C}_n\text{H}_{2n}(\text{COOH})_2$

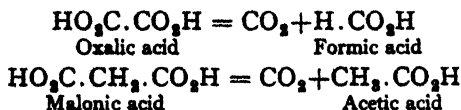
Formation.—Dibasic acids are found to some extent in nature, and may be obtained artificially by methods similar to those used for the monobasic acids (see p. 205). Chief among these are the oxidation of the corresponding glycols, aldehydes, hydroxy-acids or aldehydic acids, the hydrolysis of dicyanides, *e.g.* $\text{CN} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CN}$, or of cyano-substituted monocarboxylic acids, *e.g.* $\text{CN} \cdot \text{CH}_2 \cdot \text{COOH}$, and the acid hydrolysis of substituted acetoacetic esters (see p. 281).



Properties.—The dibasic acids are strongly acidic crystalline compounds. In most cases they dissolve readily in water, the solubility of an acid containing an uneven number of carbon atoms being greater than that of the next higher acid with an even number. A similar regularity is found in the melting-points, an acid with an even number of carbon atoms melting higher than the following member containing an odd number.

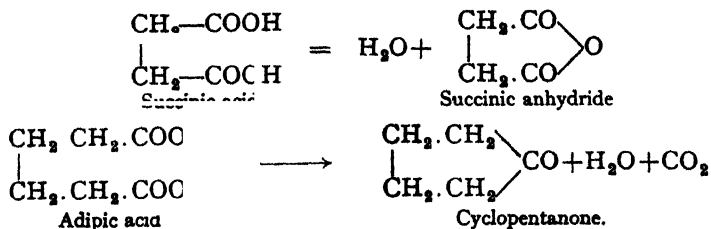
A point to be noted is the varying behaviour of the dibasic acids under the influence of heat, etc.

Oxalic acid, $\text{HOOC} \cdot \text{COOH}$, and all those homologues in which, as in the case of malonic acid, $\text{CH}_2(\text{COOH})_2$, the two carboxyl groups are attached to the same carbon atom, decompose on heating to give carbon dioxide and a monobasic acid.



On the other hand, the higher dibasic acids decompose according to *Blanc's Rule*, according to which acids with the carboxyl groups in the

1 : 3, 1 : 4, and 1 : 5 positions on distillation of their barium salts or on treatment with acetic anhydride yield anhydrides. 1 : 6-Acids lose a molecule of carbon dioxide on such treatment and give cyclic ketones.

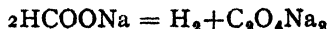


Although there are exceptions to the rule, it has been of great service in deciding between five and six-membered hydroaromatic rings. For instance, cyclopentanone can be oxidised to glutaric acid which when heated gives its anhydride, while cyclohexanone gives first adipic acid and then (as above) cyclopentanone.

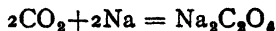
Among the higher members a number of structural isomerides are possible, according to the relative positions of the two carboxyl groups in the carbon chain.

Oxalic acid, $\text{HOOC} \cdot \text{COOH}$, occurs very extensively in the vegetable kingdom, particularly as the potassium salts in plants of the *oxalis* and *rumex* families. In the animal organism it is found as the calcium salt. It is formed during the oxidation of many organic compounds, and was formerly prepared industrially from cellulose by fusing sawdust with sodium or potassium hydroxide.

Oxalic acid is now prepared by the rapid heating of sodium formate,



and by the direct combination of carbon dioxide with sodium at 360° .



Properties.—Oxalic acid crystallises in monoclinic prisms, m.p. 101° , containing 2 mols. water of crystallisation. Oxalic acid is poisonous. When carefully heated to 150° it sublimes, but on rapid heating it decomposes partly into carbon monoxide and formic acid (see p. 207), and partly into carbon dioxide, carbon monoxide and water. These last products are obtained exclusively on warming oxalic acid with concentrated sulphuric acid or acetic anhydride.



When treated with potassium permanganate in acid solution, oxalic acid is readily oxidised to carbon dioxide and water, a reaction frequently utilised in volumetric analysis.

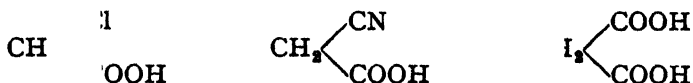


Oxalic acid and its antimony salt are used as mordants in the printing and dyeing industries. It is also employed for whitening leather, removing

ink and rust stains, bleaching and cleaning straw and stearine goods, in the manufacture of inks and the preparation of certain coal-tar dyes.

Among the more important oxalic derivatives are the following. **Diethyl oxalate**, $C_2H_5OOC.COOC_2H_5$, b.p. 186° , **Oxamic acid**,¹ $HOOC.CONH_2$, is the monoamide of oxalic acid, and is formed by heating ammonium hydrogen oxalate. **Oxamide**, $NH_2.OC.CO.NH_2$, the diamide of oxalic acid is formed in a variety of ways, such as by the action of ammonia on ethyl oxalate. It is a white powder which is almost insoluble in water.

Malonic acid, $CH_2(COOH)_2$, occurs in beetroot. It is obtained from chloroacetic acid by heating it with potassium cyanide to give cyanoacetic acid, and subsequent hydrolysis.



Malonic acid, m.p. 132° , when heated decomposes into carbon dioxide and acetic acid. This ease of decarboxylation is characteristic of substances containing two carboxyl groups attached to one carbon atom. Most other acids are decarboxylated only by heating with calcium oxide. Its esters are of great value in the synthesis of organic compounds.

The mono-nitrile, **cyanoacetic acid**, prepared as above, is a useful synthetic agent. Its ethyl ester is required in the manufacture of barbiturates.

Diethyl malonate, $CH_2(COOC_2H_5)_2$, b.p. 192° , is conveniently prepared from cyanoacetic acid by the action of alcohol and sulphuric acid, the malonic acid first produced being converted into the ester. With phosphorus pentoxide it yields the double ketene $O : C : C : O$, known as *carbon suboxide*. The latter is a liquid of powerful odour boiling at 7° .



Malonic acid itself also decomposes into carbon suboxide on heating with phosphorus pentoxide, and is recommended by Diels as the best starting material for the preparation of this compound.

Malonic Ester Synthesis.—Esters of malonic acid resemble acetoacetic ester in that—owing to the influence of the neighbouring carbonyl groups—the two hydrogen atoms of the methylene group may be replaced successively by sodium.

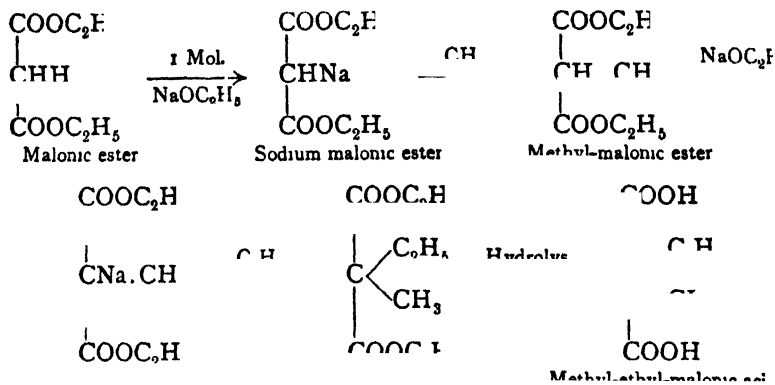


The metal can then be exchanged for other groups by bringing the sodium compound into reaction with organic halogen compounds (*e.g.*

¹ The mono-amides of dibasic acids are known generally as amic acids.

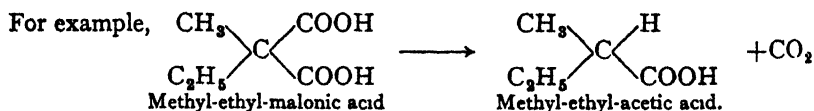
alkyl and acyl halides). As a result we have a valuable method for the preparation of dibasic acids of the general types $\text{CHX}(\text{COOH})_2$ and $\text{CXY}(\text{COOH})_2$.

The following scheme represents a typical synthesis



For further information reference should be made to the similar case of acetoacetic ester, which has been dealt with in detail.

It has already been mentioned that those dicarboxylic acids in which the two acid groups are separated by a single carbon atom readily lose carbon dioxide when heated, and pass into monobasic acids. From the dibasic acids synthesised by the above method we can therefore obtain by the action of heat substituted acetic acids of the type $\text{CH}_2\text{X} \cdot \text{COOH}$ and $\text{CH}(\text{XY}) \cdot \text{COOH}$.

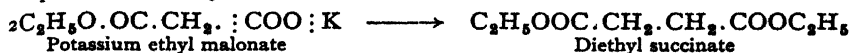


These substituted acetic acids can also be obtained by the acid hydrolysis of acetoacetic ester derivatives, as described on p. 281, but a certain amount of ketonic hydrolysis usually occurs at the same time, reducing the yield of acid. On the other hand, in malonic ester syntheses the substituted malonic acids decompose in one direction only, and it is therefore more expedient to use this method for the preparation of the homologous fatty acids.

Electrosynthesis.—Syntheses effected by electrolytic means in organic chemistry are not very numerous, but the method has been applied with great success to salts of the monoesters of dibasic acids, and of malonic acid in particular.

Brown and Walker found that on electrolysing the aqueous solution of an alkali salt of a monoester of a dicarboxylic acid (*e.g.* potassium ethyl malonate) the free carboxyl group was eliminated as carbon dioxide, and two of the residues thus produced united together, as in the Kolbe synthesis of ethane (p. 106), to form the diester of a higher dicarboxylic

acid. In this manner the more complex dibasic acids were prepared synthetically from lower homologues : *e.g.* succinic ester was obtained from potassium ethyl malonate :

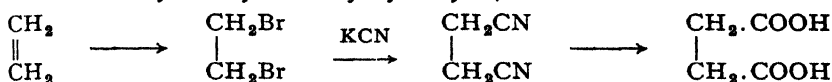


By starting from the ethyl potassium salt of a substituted malonic acid the reaction gives a substituted succinic ester, *e.g.*,

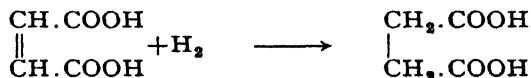


Succinic acid, $\text{HOOC}.\text{CH}_2.\text{CH}_2.\text{COOH}$, m.p. 185° , occurs in amber, in a few resins and brown coal, in many plants and in the animal organism. It is formed in small amounts during the alcoholic fermentation of sugar. It may be synthesised by the following reactions :—

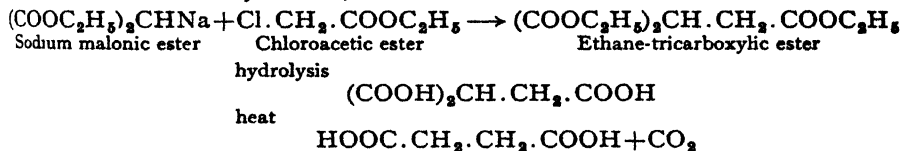
1. From ethylene cyanide by hydrolysis,



It is manufactured by this method, the cheaper ethylene dichloride being used instead of the dibromide. It is also prepared industrially by the reduction of maleic acid.

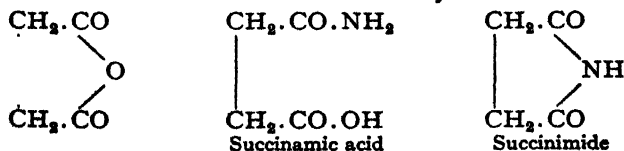


2. From malonic acid by electrolytic methods (see above); also by the "malonic ester synthesis,"



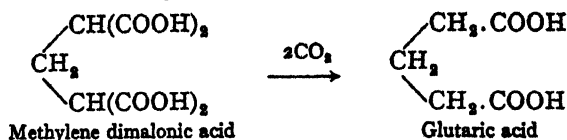
It is readily seen that alkyl-substituted succinic acids can also be obtained by this reaction, by combining alkyl-substituted sodium malonic esters, $\text{NaRC}(\text{COOC}_2\text{H}_5)_2$, with alkyl-substituted chloroacetic esters.

Succinic acid readily loses water to form **succinic anhydride** (p. 284). Such cyclic anhydrides, containing as they do 5- or 6-membered rings, are typical ring-closure products. Ammonium succinate on heating affords **succinimide**, m.p. 126° , which is also obtained via *succinamic acid* by the action of ammonia on succinic anhydride.



The contiguous acyl groups render the hydrogen atom of the imino acidic; Succinimide as a result forms a potassium salt.

Glutaric acid, $\text{COOH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$, m.p. 97° , may be prepared from trimethylene bromide *via* the cyanide $\text{CN} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CN}$, or from *methylene dimalonic acid* by loss of CO_2 .

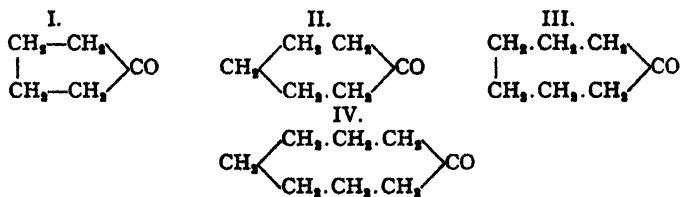


Adipic acid, $\text{COOH} \cdot (\text{CH}_2)_4 \cdot \text{COOH}$, m.p. 153° , was first obtained by the oxidation of fat (Latin *adepts*, fat) by means of nitric acid, and is best prepared by oxidising cyclohexanol with concentrated nitric acid. It is prepared in this way on the industrial scale for use in the manufacture of *nylon*. The barium salt on dry distillation yields *cyclo-pentanone* (I), together with barium carbonate.

Normal pimelic acid, $\text{COOH} \cdot (\text{CH}_2)_5 \cdot \text{COOH}$, is conveniently prepared from 1 : 5-dichloropentane (p. 721) *via* the dicyanide. It melts at 103° , and on distillation of the calcium salt yields *cyclo-hexanone* (II). It is also obtained as a degradation product of the alkaloids atropine and cocaine, thus showing that these contain the carbon chain of *n*-pimelic acid in the form of a seven-membered ring.

Suberic acid, $\text{COOH} \cdot (\text{CH}_2)_6 \cdot \text{COOH}$, m.p. 140° , occurs in the skin of the toad, and is prepared by the oxidation of cork (Latin *suber*, cork). Brown and Walker showed that the ester of this acid is formed by the electrolysis of ethyl potassium glutarate. It may also be synthesised by the action of magnesium and carbon dioxide on trimethylene bromide in dry ethereal solution. When the calcium salt is distilled, *cyclo-heptanone* or *suberone* (III) is obtained.

Azelaic acid, $\text{COOH} \cdot (\text{CH}_2)_7 \cdot \text{COOH}$, m.p. 107° , is formed by the oxidation of oleic acid with nitric acid, or synthetically from sodium acetoacetic ester and pentamethylene bromide. On distillation with lime it gives *cyclo-octanone* (IV) but much better yields are obtained by use of the thorium salt.



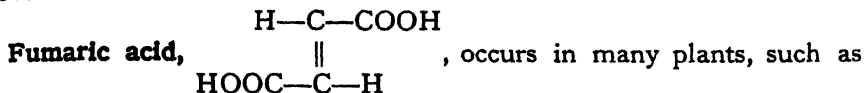
Sebacic acid, $\text{COOH} \cdot (\text{CH}_2)_8 \cdot \text{COOH}$, m.p. 133° , is obtained when stearic acid, spermaceti or castor oil is oxidised with nitric acid.

II.—UNSATURATED DIBASIC ACIDS

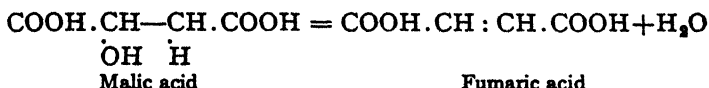
gta.

acid in those dibasic acids in which ethylene linkages are present may be prepared as dicarboxylic derivatives of the olefins, a classification which Brown and Walker have shown to be very useful in the study of an alkali salt in connection with their chemical behaviour. As acids they form ethyl malonate) the similar to those of the saturated dibasic acids described above, and two of the residues they possess additive properties, uniting with two atoms of hydrogen to form ethane (p. 109), or with one molecule of hydrogen halide. The representatives in this group are *fumaric* and *maleic*.

acids, $C_4H_4O_4$, both of which have been shown to be symmetrical dicarboxylic derivatives of ethylene. These two acids form one of the best known and most completely investigated cases of geometrical isomerism among symmetrically substituted ethylene derivatives. This type of isomerism has already been discussed in the theoretical section of this book (see p. 44). Structurally, fumaric and maleic acids are identical since both yield the same products with various reagents. With sodium amalgam, for example, both are reduced to succinic acid. The isomerism of the acids, therefore, must have a configurational origin as suggested above.



Iceland moss and *Fumaria officinalis*. It is formed as the chief product of reaction when malic acid is heated for a considerable time at 140° to 150° ,

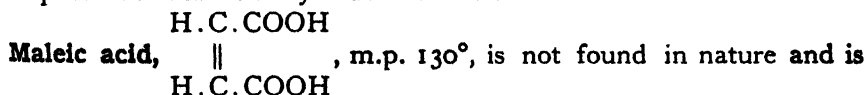


Fumaric acid

and also when hydrogen halide is removed from monochloro- or monobromo-succinic acid by boiling in aqueous solution. It may also be obtained by the condensation of glyoxalic acid and malonic acid in the presence of pyridine.



Fumaric acid is sparingly soluble in cold water, from which it crystallises in small white needles. Under ordinary pressure it possesses no melting-point, but sublimes at 200° . At a higher temperature it partially decomposes into maleic anhydride and water.



prepared on the industrial scale by the catalytic air-oxidation of benzene. The anhydride is the chief product of reaction when malic acid is rapidly heated to a high temperature, and is readily converted into the acid by treatment with water. Maleic acid is also obtained from fumaric acid by various methods (see over).

Stability and Interconversion of Fumaric and Maleic Acids

Fumaric acid is more stable than maleic acid and this is shown by its smaller heat of combustion. It would therefore be expected that the acid would possess the *trans*-configuration, in which the two carboxyl groups with similar charges are as far removed from each other as possible. This is confirmed experimentally (see over).

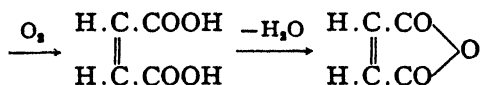
It is characteristic of geometrical isomerides that under certain

conditions they are readily converted into one another. It is impossible to generalise, but it may be said that frequently chemical reagents or heat give the more stable isomer, while ultra-violet light or sunlight converts the stable into the labile form. Maleic acid passes without difficulty into fumaric acid if heated alone or in solution or by the action of hydrogen halides, etc. A striking example is the conversion of methyl maleate in a few seconds into a crystalline mass of methyl fumarate by a trace of piperidine.¹ On the other hand fumaric acid is converted to maleic acid on exposure to ultra-violet light.

Determination of the Configuration of Geometrical Isomers in the Ethylene Series

There is no universal method for determining the configuration of *cis-trans* isomers of the olefinic type. Some of the most reliable are given here. (See also p. 215.)

Relation to Cyclic Compounds.—The ease with which maleic acid forms an anhydride, coupled with the fact that fumaric acid yields none, is sufficient to characterise the former without doubt as the *cis*-modification, since the carboxyl groups are in the neighbouring position necessary for anhydride formation.



This configuration is corroborated by the oxidation of benzoquinone (in which the carbonyl groups are "fixed" in the *cis*-positions) to maleic acid but not to fumaric acid.

In anhydride formation we have a general means of determining the configuration of unsaturated dibasic acids of the type $\text{COOH.CR}=\text{CR.COOH}$. As maleic acid is the simplest *cis*-acid, compounds of similar configuration are sometimes known as "maleinoid forms," and those corresponding to fumaric acid as "fumaroid forms."

Among numerous examples of this kind may be mentioned the next higher homologues of fumaric and maleic acid, both of the structural formula $\text{COOH.C}(\text{CH}_3)=\text{CH.COOH}$. Of these, the maleinoid form is called *citraconic acid* and the fumaroid form *mesaconic acid*.

Physical Properties.—One of the most decisive means of distinguishing between the *cis*- and *trans*-forms of the compounds containing simple polar groups is by a comparison of their dipole moments (see p. 72). The method, however, must be applied with care to more complex radicals

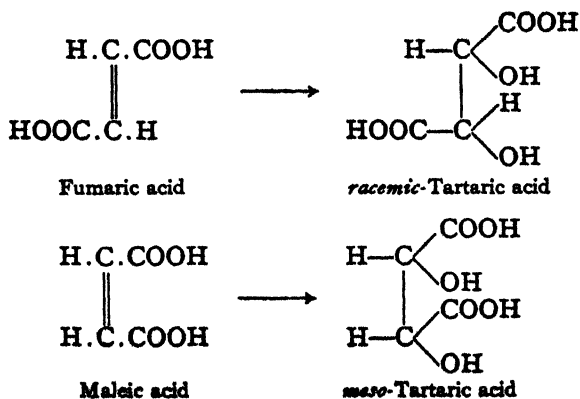
¹ Clemo and Graham, *J.*, 1930, 213.

such as the carboxyl. This is shown by diethyl fumarate ($\mu = 2.38 \times 10^{-18}$ e.s.u.) which has a smaller dipole moment than diethyl maleate ($\mu = 2.54 \times 10^{-18}$ e.s.u.).

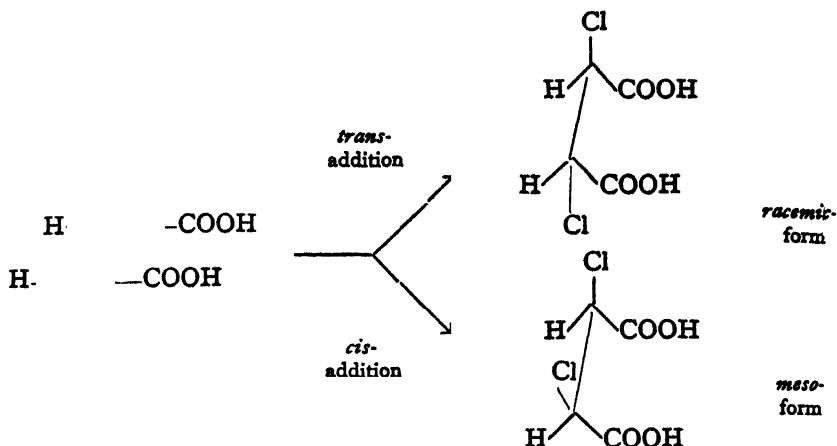
Similar caution must be exercised in the interpretation of other physical properties. Some of these are valueless for configurational determinations, but a number serve as useful guides. The *trans*-isomer usually has the higher melting-point, the lower heat of combustion, and (with acids) the lower ionisation constant. These differences are shown in the following table. The lower heat of combustion is indicative of greater stability, *i.e.* the *cis*-isomers are less stable than the *trans*-. This is in agreement with the factors governing the inter-conversion of *cis*- and *trans*-isomers. The *trans*- compounds yield the *cis*-isomers by supplying energy in the form of ultra-violet radiation. The reverse change is generally effected by chemical methods.

Acid	m.p.	K_a	Heat of Combustion K.Cal./molecule
Fumaric (<i>trans</i>) . . .	300°	9.3×10^{-4}	320
Maleic (<i>cis</i>) . . .	130°	1.17×10^{-2}	326
Crotonic (<i>trans</i>) . . .	72°	2×10^{-5}	478
Isocrotonic (<i>cis</i>) . . .	15°	3.6×10^{-5}	486
Elaidic (<i>trans</i>) . . .	44°	...	2664
Oleic (<i>cis</i>) . . .	13° and 16°	...	2682

Conversion to Saturated Compounds.—Another but much less certain method of determining configuration is to convert the isomerides into symmetrical derivatives of ethane, containing two asymmetric carbon atoms. On the assumption that such additions are entirely *cis* (van't Hoff, Wislicenus), the *trans*-form would be expected to give the corresponding racemic compound. On the other hand, the *cis*-form would be expected to lead to the formation of an inactive, internally-compensated (*meso*-) compound. Oxidation with permanganate, for instance, has been shown to involve *cis*-addition, fumaric acid giving *racemic*-tartaric acid and maleic acid giving *meso*-tartaric acid.



Later workers showed, however, that many additions at the double bond are chiefly *trans*. For example, maleic acid gives mainly a *racemic*-product on chlorination, showing that *trans*-addition is the main reaction.



Similarly fumaric acid gives mainly the *meso*-acid by *trans*-addition of chlorine. Again, it was shown by McKenzie that the di-bromo-succinic acid formed by addition of bromine to maleic acid is the racemic compound, and not the meso-compound. Unless then the mechanism of addition is understood, such reactions are unreliable for the determination of configuration.

The Diels-Alder reaction (p. 450) appears, however, to involve only *cis*-addition and is therefore of general application.

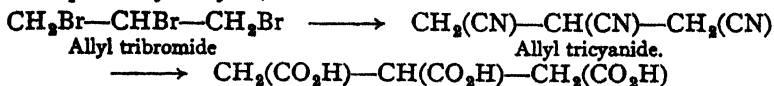
Dibasic acids are also known containing triple bonds in the molecule. The simplest of these is **acetylene dicarboxylic acid** $\text{COOH} \cdot \text{C} \equiv \text{C} \cdot \text{COOH}$, which crystallises with two molecules of water, and is prepared from dibromo-succinic acid by treatment with alcoholic potash. When the potassium hydrogen salt of this acid is warmed with water it decomposes into carbon dioxide and potassium propiolate, $\text{CH} \cdot \text{C} \cdot \text{COOK}$ (see p. 219).

It is to be noted that the acetylene carboxylic acids are comparatively strong acids, as may be seen from their dissociation constants. A triple bond, and to a less extent a double bond, therefore leads to an increase of acidic character.

III.—ACIDS OF HIGHER BASICITY

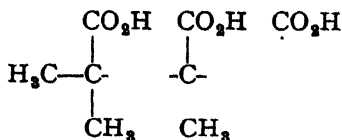
With regard to the constitution of acids of higher basicity, it is to be remembered that, as in the case of certain other poly-substituted compounds already discussed, the presence of more than one carboxyl group attached to the same carbon atom leads to instability. No compound is known containing more than two carboxyl groups in this state of combination.

Tricarballic acid, $\text{CH}_2(\text{CO}_2\text{H})\cdot\text{CH}(\text{CO}_2\text{H})\cdot\text{CH}_2(\text{CO}_2\text{H})$, occurs in unripe beetroots. It may be formed synthetically by various reactions, *e.g.* from allyl tribromide, by conversion into the tricyanide and subsequent hydrolysis,

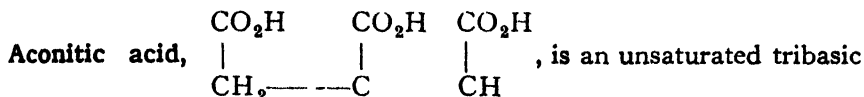


A monohydroxy derivative of this acid is citric acid, which is dealt with later.

Camphoronic acid, $\alpha\beta$ -trimethyl-tricarballic acid, m.p. 135° , is



formed by the oxidation of camphor. The determination of its constitution by Perkin and Thorpe provided valuable evidence in connection with the structure of camphor.



acid, and is formed by removing the elements of water from citric acid. On reduction it takes up two atoms of hydrogen and is converted into tricarballic acid.

XVI

Polybasic Acids containing Hydroxy, Amino, Aldehydic and Ketonic Groups

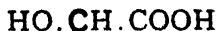
In chemical behaviour and general methods of preparation these compounds resemble the corresponding derivatives of the monobasic acids previously described.

Dibasic Hydroxy Acids

The simplest compounds of this class are derived from malonic acid.

Tartronic acid, *hydroxy-malonic acid*, $\text{COOH}\cdot\text{CHOH}\cdot\text{COOH}$, is formed in small quantities from chloro- or bromo-malonic acid by replacing halogen with hydroxyl, or from glycerol by oxidation with permanganate. As will be seen later, *mesoxalic acid* may be regarded as *dihydroxy-malonic acid*.

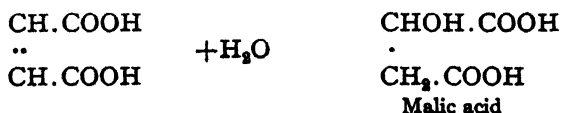
Of far greater importance than the hydroxy derivatives of malonic acid are those of succinic acid, namely malic and tartaric acids.



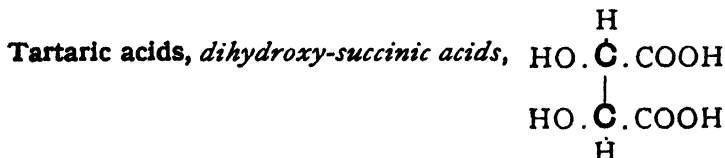
Malic acid, *hydroxy-succinic acid*, $\begin{array}{c} | \\ \text{CH}_2\cdot\text{COOH} \end{array}$, is widely distributed in the vegetable kingdom, occurring for example in sour apples,

grapes and the berries of the mountain ash. It is best obtained from the last source. As may be seen from the above formula it contains an asymmetric carbon atom, and may therefore exist in (+)-, (−)-, and *r*-forms. The acid obtained from the above natural sources is the *laevorotatory* form, m.p. 100°, which forms deliquescent needles, and on heating yields either fumaric acid or maleic anhydride according to the conditions used.

r-Malic acid is manufactured by the addition of water to the ethylenic bond of maleic acid by means of sulphuric acid.



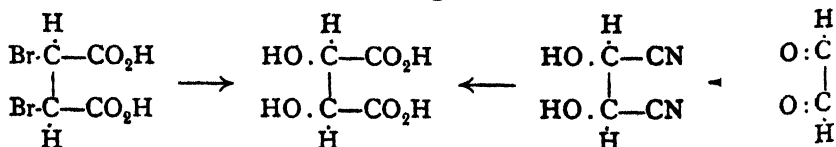
Its structure follows from this synthesis and reduction by hydriodic acid to succinic acid.



Special interest attaches to the tartaric acids, because the investigation of these compounds by Pasteur led to the first real advances in our knowledge of optical activity. Even to-day these acids are the best known and most completely investigated examples of compounds containing two similar asymmetric carbon atoms.

As explained in the introductory section of this book (p. 30), there are in agreement with theory four stereoisomeric tartaric acids, distinguished as *dextro-tartaric acid*, *laevo-tartaric acid*, *racemic acid* and *meso-tartaric acid* respectively. The following description deals in the main with their chemical properties, and for a discussion of their stereochemical differences reference should be made to the general section.

The structural formula quoted above has been verified experimentally by the synthesis of the inactive acids, *e.g.* from the silver salt of dibromosuccinic acid by boiling with water, or from glyoxal by addition of hydrogen cyanide and hydrolysis of the resulting nitrile :



The formula assigned is in harmony with the chemical properties of tartaric acid. Thus the acid is reduced by hydriodic acid to malic and succinic acids and with hydrobromic acid yields dibromosuccinic acid.

x. Dextro-tartaric acid, L(+)-tartaric acid,¹ is the common form of

¹ For the meaning of the symbols D and L see p. 28.

tartaric acid. It is found in different varieties of fruit, particularly in grapes, as the potassium hydrogen salt, $\text{KHC}_4\text{H}_4\text{O}_6$. The crude salt, known as *argol* or *tartar*, is an important by-product of the wine industry. Owing to its insolubility in dilute alcohol, it separates during fermentation in hard brown crusts in the vats and storage tubs. It serves as the raw material for the technical preparation of tartaric acid, which is carried out by conversion into the calcium salt followed by decomposition with dilute sulphuric acid.

L-Tartaric acid is readily soluble in water and alcohol. The solution in water is dextro-rotatory. When rapidly heated the acid melts at 167° to 170° . Heated with a little water to 175° , it gives a mixture containing much racemic and a little meso-tartaric acid; at 165° , on the other hand, these proportions are reversed.

Inactivation of this kind is frequently met with among optically active compounds. The partial or complete conversion of optically active substances into inactive mixtures of the same constitution is known as *racemisation*, and may be effected with varying degrees of ease under the influence of heat, acids, alkalis or other reagents (see p. 31). In a few cases the change proceeds of itself in the apparently pure compound, the optical activity being completely lost in the course of time; the phenomenon is then termed *auto-racemisation* (see p. 31).

When heated with hydriodic acid reduction takes place, first to malic acid and finally to succinic acid.

Tartaric acid, cream of tartar and tartar emetic are used as mordants in dyeing and printing. The acid is also employed in the preparation of effervescing drinks, baking powder, and in the manufacture of artificial wine.

Salts of tartaric acid, tartrates.—*Sodium potassium tartrate, Rochelle salt*, $\text{KNaC}_4\text{H}_4\text{O}_6 + 4\text{H}_2\text{O}$, is prepared from cream of tartar and sodium carbonate. It forms clear crystals, readily soluble in water. *Potassium antimonyl tartrate, tartar emetic*,



is obtained by boiling cream of tartar with antimony oxide. It is fairly easily soluble in water and acts as an emetic. *Fehling's solution*, containing copper sulphate, Rochelle salt and caustic soda,¹ is a useful reagent. When the deep blue solution is warmed with compounds possessing reducing properties a yellowish red precipitate of cuprous oxide is formed.

2. *Laevo-tartaric acid, D(—)-tartaric acid*, is obtained by the resolution of racemic acid (see p. 33). In its chemical and nearly all its physical properties the D-acid is identical with the L-acid. It differs in rotating the plane of polarisation to the left to the same degree as L-tartaric acid rotates it to the right.² The salts of the two acids are very similar and generally isomorphous, but show opposed hemihedral facets. Salts with optically active bases, however, differ also in solubility.

¹ The presence of tartaric acids prevents the precipitation of many metals by caustic soda.

² Isomeric L- and D-modifications often differ in their physiological action. D-Tartaric acid, for example, is much more poisonous than the L-acid.

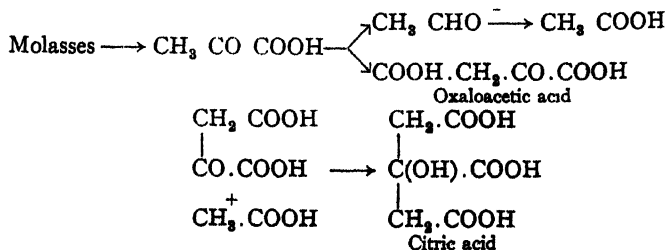
3. **Racemic acid**, *DL-tartaric acid*, sometimes occurs with the (+)-acid in grape juice and can be isolated from the argol mother-liquors. Its synthesis has already been mentioned, also its formation by oxidation of fumaric acid. It is composed of equimolecular proportions of (+)- and (—)-tartaric acids, and is formed by mixing solutions of these compounds.¹ The crystalline acid has the composition $2C_4H_4O_6 + 2H_2O$. Methods of resolving racemic acid into the active components have already been described on p. 33.

Racemic acid differs from the D- and L-acids in its optical inactivity and in forming rhombic prisms. It is less soluble than the active acids. On heating to 110° , water of crystallisation is expelled, and the anhydrous substance finally melts with effervescence at 205° to 206° . The salts, known as racemates, resemble those of tartaric acid but show no hemihedral facets.

4. **Meso-tartaric acid**, $C_4H_4O_6 + H_2O$, is formed by oxidation of maleic acid and by heating L-tartaric acid with water. It resembles racemic acid in being optically inactive, but unlike this compound cannot be resolved into active components. Meso-tartaric acid is therefore said to be *internally compensated* and racemic acid to be *externally compensated*. The anhydrous acid melts at 143° , considerably below the figure for racemic acid

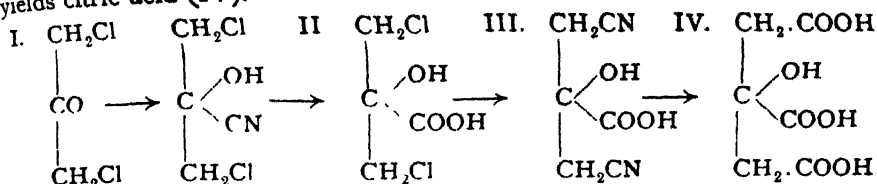
Tribasic Hydroxy Acids

Citric acid occurs in the free state in lemons, oranges, currants and other fruit. It is prepared on the large scale by the fermentation of carbohydrates (in the form of molasses) by specific fungi, and this method has largely displaced production from lemons and limes in which Italy used to provide 90 per cent. of the world's supply. Details of the method are not available, though low *pH* is essential since high *pH* favours the formation of oxalic acid. The mechanism of the fermentation is still uncertain, but Krebs has advanced an attractive theory in which incomplete fermentation gives rise to pyruvic acid. One molecule of this acid is decarboxylated to acetaldehyde which is oxidised to acetic acid, and a second molecule is carboxylated to *oxaloacetic acid*. In the final stage the acetic acid condenses with the oxaloacetic acid to give citric acid.



¹ From cryoscopic measurements it appears that racemic acid in solution is decomposed into its components. The experiments of Cotton, however, indicate that some copper racemate exists as such in solution (see p. 28).

Synthetically, citric acid may be obtained from symmetrical dichloro-acetone (I), by treating it with hydrogen cyanide and hydrochloric acid to give dichloro-acetonic acid (II), and converting this by means of potassium cyanide into dicyano-acetonic acid (III), which on hydrolysis yields citric acid (IV).

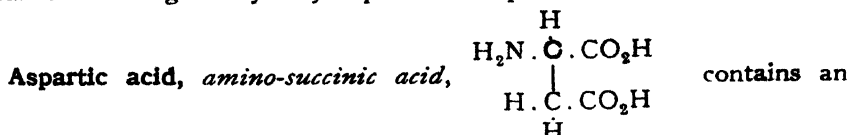


On heating it becomes anhydrous at 130° and melts at 153° , and above this temperature parts with water to form *aconitic acid* (see p. 293). If warmed carefully with concentrated sulphuric acid it decomposes into carbon monoxide, water and *acetone dicarboxylic acid*, $\text{COOH} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{COOH}$.

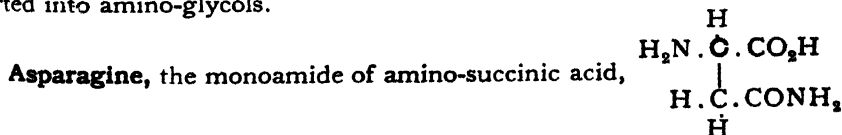
Citric acid is employed as a mordant in dyeing, and is used in the manufacture of lemonade.

Polybasic Amino-Acids

Certain representatives of this class are of interest owing to their occurrence among the hydrolytic products of proteins.



asymmetric carbon atom and exists in three modifications, of which *L-aspartic acid* is the most important. It is found in beet molasses, and is formed as a hydrolysis product by the action of various reagents on animal and vegetable proteins. When treated with nitrous acid it is converted into *L-malic acid*, the amino group being replaced by a hydroxy group. By means of the Grignard reaction aspartic esters may be converted into amino-glycols.



occurs usually as the laevo-rotatory variety in a number of plants, particularly in the embryo. It is found in asparagus, beetroot, and in large amounts in the seeds of germinating lupins. The dextro-rotatory form is also present in the latter source. Optically active asparagines crystallise in clear rhombic crystals, showing hemihedral facets; they differ in taste, (+)-asparagine being sweet, and the (−)-compound decidedly insipid.

On boiling with acids the amido group is hydrolysed and aspartic acid formed.

Glutamic acid, α -amino-glutaric acid, $\text{CH}_2 < \begin{matrix} \text{CH}(\text{NH}_2).\text{COOH} \\ \text{CH}_2.\text{COOH} \end{matrix}$, 1

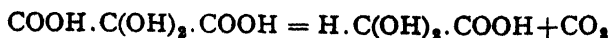
formed together with aspartic acid by the hydrolysis of proteins with boiling dilute sulphuric acid; *e.g.* it constitutes about 30 per cent. of the crystalline products obtained from casein. The highest content (*ca* 40 per cent.) of glutamic acid is given by certain plant proteins, the *prolamines*, occurring in grain. Glutamic acid is isolated by means of its very sparingly soluble hydrochloride. The acid and many of its salts are easily converted (*e.g.* even on heating to 185°) into pyrrolidone carboxylic acid, and are thus closely related to the cyclic amino-acid *proline*.

Glutamine, the monoamide of glutamic acid, $\text{C}_5\text{H}_9(\text{NH}_2)(\text{CONH}_2)(\text{COOH})$, is the nearest homologue of asparagine. In the inactive form it is found associated with the latter in beetroot, the embryo of the pumpkin and other plants.

Hydroxy - glutamic acid, α - amino - β - hydroxy - glutaric acid $\text{COOH}.\text{CH}(\text{NH}_2).\text{CHOH}.\text{CH}_2.\text{COOH}$, was isolated from the hydrolysis products of proteins by Dakin, by his method of extraction with butyl alcohol. It is crystalline, dissolves very readily in water, and on reduction with hydriodic acid yields glutamic acid. With phenols and concentrated sulphuric acid it gives various colour reactions.

Dibasic Aldehydic and Ketonic Acids

Mesoxalic acid, $\text{CO}(\text{COOH})_2 + \text{H}_2\text{O}$ or $\text{C}(\text{OH})_2(\text{COOH})_2$, is derived from malonic acid, and its constitution presents a problem similar to that of glyoxalic acid (p. 273). The compound cannot be obtained without the molecule of water quoted in the above formulæ, and it must therefore be assumed that this does not occur merely as water of crystallisation, but is united to the keto-group to form two hydroxyl groups. Nevertheless, the ketonic nature of the compound is clearly shown in its power of combining with alkali bisulphite, phenylhydrazine and hydroxylamine, and also in its behaviour on reduction. Nascent hydrogen, for example, converts it into *tartronic acid*, $\text{CHOH}(\text{COOH})_2$, containing a secondary alcoholic grouping. When boiled in aqueous solution, mesoxalic acid evolves carbon dioxide and yields glyoxalic acid, a reaction which is most readily explained by the hydroxy acid formula.



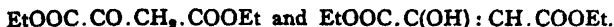
The ethyl ester of mesoxalic acid is actually known to exist in the two forms, $\text{C}(\text{OH})_2(\text{COOEt})_2$ and $\text{CO}(\text{COOEt})_2$.

Mesoxalic acid is most conveniently prepared by heating dibromomalonic acid with sodium hydroxide. It crystallises in deliquescent prisms, m.p. 121°.

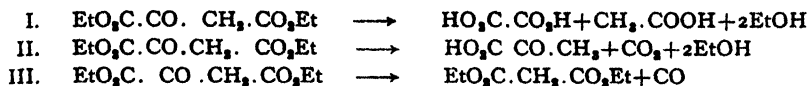
Oxalo-acetic ester is produced by the condensation of oxalic and acetic esters: for the mechanism of this reaction, see p. 274 *et seq.*



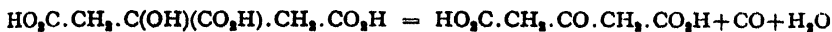
The ester is a colourless oil which, like acetoacetic ester, may be regarded as mixture of two tautomeric forms, viz.,



It undergoes hydrolysis in two ways. When boiled with alkalis, "acid hydrolysis" (I) takes place with the formation of oxalic acid, acetic acid and alcohol. On the other hand, boiling with dilute sulphuric acid brings about "ketonic hydrolysis" (II) into carbon dioxide and pyruvic acid. When heated alone, carbon monoxide is evolved and malonic ester formed (III).



Acetone dicarboxylic acid, *β*-keto-glutaric acid, $\text{HOOC.CH}_2\text{CO.CH}_2\text{COOH}$, is obtained from citric acid by warming it with fuming sulphuric acid,



or by oxidation with permanganate.

XVII

Carbohydrates¹

The carbohydrates are of the greatest importance both from the theoretical and from the practical standpoint. As foodstuffs they undoubtedly rank in the first place, and with the single exception of the proteins, no class of organic compounds is of such value in the study of the chemical process which takes place in plant and animal organisms. They play, for example, a fundamental role in muscular contraction and fermentation. Of the industrial processes based on the chemistry of the carbohydrates it is sufficient to mention only the manufacture of textiles, paper, explosives and beer.

Carbohydrate chemistry is a huge field which has attracted the attention of a large number of investigators, notable among whom were Emil Fischer, Sir W. N. Haworth, Sir J. C. Irvine, and Professor Thomas Purdie who, with their colleagues at the Universities of Berlin, Birmingham and St Andrews carried out the fundamental pioneer work on the subject.

The term carbohydrate was originated in the belief that naturally occurring compounds of this class could be represented by a general formula $\text{C}_x(\text{H}_2\text{O})_y$. Glucose thus has the formula $\text{C}_6\text{H}_{12}\text{O}_6$, cane sugar $\text{C}_{12}\text{H}_{22}\text{O}_{11}$, etc. On that basis, however, the important methylpentoses

¹ D. J. Bell, *Carbohydrate Biochemistry* (University Tutorial Press), 3rd edition, 1952.
 G. V. Percival, *Structural Carbohydrate Chemistry* (Miller), revised edition, 1953. W. W.
 K. M. Goepf, Jr., *Chemistry of the Carbohydrates*. J. Honeyman, *An Introduction to the Chemistry of the Carbohydrates* (Oxford University Press).

(6-deoxyhexoses) such as rhamnose, $C_6H_{12}O_6$, and other "deoxy" sugars would be excluded. The retention of the term carbohydrate is therefore a matter of convenience rather than of precise definition.

The first division of the carbohydrates is into three main classes according to their complexity, viz. :

- A. *Monosaccharides*, e.g. arabinose, $C_5H_{10}O_5$, glucose, $C_6H_{12}O_6$.
- B. *Di- and tri-saccharides*, e.g. cane sugar, $C_{12}H_{22}O_{11}$, raffinose $C_{18}H_{32}O_{16}$; the compound sugars containing from two to six sugar units are called *oligosaccharides*.
- C. *Polysaccharides*, e.g. starch, cellulose, $(C_6H_{10}O_5)_n$.

Owing to their sweet taste and crystalline character the mono-, di- and tri-saccharides are generally grouped together under the name of *sugars*. Sugars of the glucose group, $C_6H_{12}O_6$, contain two hydrogen atoms less than the hexahydric alcohols, $C_6H_{14}O_6$ (see p. 268), and from their chemical character are divided into *aldehydic alcohols* and *ketonic alcohols*. A simpler example of an aldehydic alcohol is glycollic aldehyde, $CH_2OH \cdot CHO$, and of a ketonic alcohol, dihydroxy-acetone, $CH_2OH \cdot CO \cdot CH_2OH$. The character of a monosaccharide, originally associated with the presence of six carbon atoms in the molecule, is nowadays determined mainly by its constitution as an aldehydic alcohol containing the group $-CHOH \cdot CH : O$, or as a ketonic alcohol with the group $-CO \cdot CH_2OH$. In this class are included not only those compounds with six carbon atoms, but many with a smaller or greater number than this. A further distinction is drawn between aldehydic and ketonic sugars by use of the terms *aldoses* and *ketoses*. The number of oxygenated carbon atoms present in the molecule is indicated by adding the necessary prefix to the termination *-ose*. In this way monosaccharides are subdivided into the smaller classes of *bioses*, *trioses*, *tetroses*, *pentoses*, *hexoses*, *heptoses*, *octoses* and *nonoses*. Since, however, the members of these groups may be either aldehydes or ketones, this is expressed by use of the prefix *aldo-* or *keto-* respectively. For example, glyceric aldehyde, $CH_2OH \cdot CHO$, is an *aldotriose*, and dihydroxy-acetone, $CH_2OH \cdot CO \cdot CH_2OH$, a *ketotriose*.

Oligosaccharides and polysaccharides appear to be anhydrides or ether derivatives of the monosaccharides. If they are formed from 2 mols. of the monosaccharide by loss of 1 mol. water they are termed *disaccharides*, e.g. cane sugar, $C_{12}H_{22}O_{11}$. Raffinose, $C_{18}H_{32}O_{16}$, is a *trisaccharide* formed from three monosaccharide molecules by elimination of 2 mols. water. Generalising these formulæ, we obtain $nC_6H_{12}O_6 - (n-1)H_2O$. If n is very large, the factor $n-1$ approximates to n , and we have

$$nC_6H_{12}O_6 - nH_2O = n(C_6H_{12}O_6 - H_2O) = n(C_6H_{10}O_5)$$

The latter is the formula for the higher polysaccharides, including starch and cellulose. All these substances undergo hydrolysis with acids, taking up water to form monosaccharides.

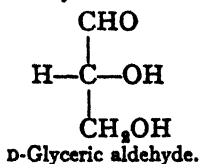
I.—MONOSACCHARIDES

The number of monosaccharides known is in the neighbourhood of seventy, of which twenty occur in nature and the remainder are synthetic. The existence of such a large number of compounds is due to the presence of asymmetric carbon atoms within the molecules. Aldohexoses, for example, which include glucose, a sugar of great historical and practical interest, contain no less than four asymmetric atoms, each of which may be present in either the D- or L-configuration. It has already been shown on p. 29 how rapidly the number of stereoisomerides increases with each additional asymmetric atom.

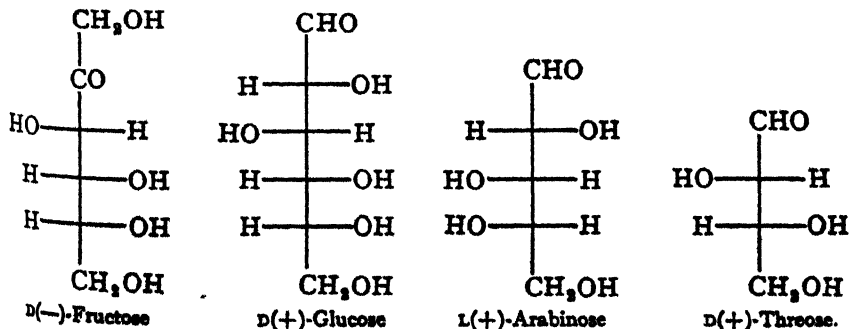
A list of the best known monosaccharides is given below.

<i>Biose</i>	$\text{CH}_2\text{OH} \cdot \text{CHO}$, glycollic aldehyde.
<i>Trioses</i>	1. $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHO}$, glyceric aldehyde. 2. $\text{CH}_2\text{OH} \cdot \text{CO} \cdot \text{CH}_2\text{OH}$, dihydroxy-acetone.
<i>Tetroses</i>	$\text{CH}_2\text{OH} \cdot (\text{CHOH})_2 \cdot \text{CHO}$, erythrose.
<i>Pentoses</i>	$\text{CH}_2\text{OH} \cdot (\text{CHOH})_3 \cdot \text{CHO}$, arabinose, xylose, ribose.
<i>Methyl-pentose</i>	$\text{CH}_3 \cdot (\text{CHOH})_4 \cdot \text{CHO}$, rhamnose.
<i>Hexoses</i>	1. $\text{CH}_2\text{OH} \cdot (\text{CHOH})_4 \cdot \text{CHO}$, glucose, gulose, mannose, galactose, talose. 2. $\text{CH}_2\text{OH} \cdot (\text{CHOH})_3 \cdot \text{CO} \cdot \text{CH}_2\text{OH}$, fructose, sorbose.
<i>Heptoses</i>	$\text{CH}_2\text{OH} \cdot (\text{CHOH})_5 \cdot \text{CHO}$, glucoheptose.

An explanation is required as to the way in which the optical isomerides are named. In accordance with a suggestion of Fischer, the structure of the sugars was, wherever possible, referred back to that of the active glucoses. This method led to ambiguities in the gulose-idose series and the convention now in use is due to Rosanoff¹ (see p. 237), who suggested that (+)-glyceric aldehyde should be represented empirically as



and that all members of the D-series of sugars should be regarded as built up from it by the Kiliani synthesis (p. 306). This is illustrated by the following formulæ and by the table on p. 317, in which the terminal

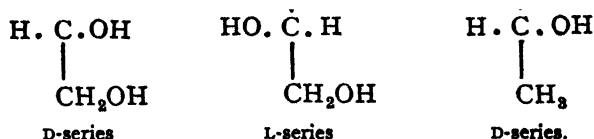


¹ M. A. Rosanoff, *J.A.C.S.*, 1906, 28, 114.

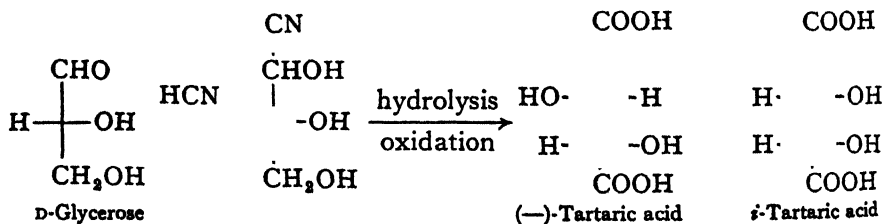
aldehydic (or hydroxymethyl ketonic) group is written uppermost and the links binding the H and OH addenda are assumed to be inclined from the chain of central carbon atoms towards the observer. In the following pages the asymmetric carbon atoms are omitted and simplified projection formulæ employed.

According to this convention a sugar belongs to the D-series when the hydroxyl group on the carbon atom adjacent to the primary alcohol group is on the right. It must be emphasised that this configurational representation as D and L bears no relation to the actual sign of the rotation (*cf.* D-fructose, which is strongly *laevo*-rotatory, and L-arabinose, which is *dextrorotatory*). The actual sign of the rotation in water at equilibrium may be indicated as above by the signs (+) and (−); in addition the prefix DL indicates a racemic and *i* a meso form.

The Rosanoff convention is also applied to the methyl pentoses and to other derivatives of the monosaccharides,



Wohl¹ later prepared (+)-glyceric aldehyde and converted it into a mixture of (−) and *meso*-tartaric acids by way of the cyanhydrin and oxidation.



This result shows that (+)-glycerose (glyceric aldehyde) is configurationally related to the D-series of sugars, since (−)-tartaric acid had also been obtained by Maquenne (1901) by oxidising D-threose, the tetrose produced by the Wohl degradation (p. 305) of D-xylose, the relationship of which to the hexoses having already been established by the work of Fischer.²

It may be added, however, that whilst it is perhaps fortunate that (+)-glycerose is genetically related to the D-series a contrary result would not have diminished the value of Rosanoff's contribution in bringing order to the relationships within the sugar group, for his convention was proposed without regard to the actual sign of the rotation of D-glycerose and is independent of it.

¹ A. Wohl and K. Freudenberg, *Ber.*, 1923, 56, 309. 1941, 18, 353.

² C. S. Hudson, *J. Chem. Ed.*,

General Properties and Methods of Formation

The monosaccharides are sweet-tasting compounds, the chemical behaviour of which may be deduced from their structure as aldehydic or ketonic alcohols.

As alcohols they unite readily with acids to form **esters**, *e.g.* acetic anhydride converts them into acetyl derivatives, and with nitric acid at 0° they form nitrates. The *phosphoric esters of pentoses and hexoses* are of great physiological importance, the former as disruption products of many nucleic acids (p. 373) and the latter as being essential for the biological degradation of carbohydrates, *e.g.* in alcoholic fermentation and during muscular effort (see pp. 334 and 335). With inorganic bases such as sodium hydroxide or strontium hydroxide the monosaccharides and disaccharides yield *derivatives*,¹ those from glucose, for example, being known as glucosates.

As aldehydes or ketones they are characterised by numerous reactions, only the more important of which need be quoted. On reduction they take up two atoms of hydrogen and pass into the corresponding alcohols; from a pentose is obtained a pentitol or pentahydric alcohol, and from a hexose a hexitol or hexahydric alcohol. On oxidation they yield carboxylic acids. Cautious oxidation converts aldoses first into the corresponding monocarboxylic acids containing the same number of carbon atoms, aldopentoses being transformed into pentonic acids, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_3 \cdot \text{COOH}$, and aldohexoses into hexonic acids, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_4 \cdot \text{COOH}$. With stronger oxidising agents the process may go further and hexoses, for example, may be oxidised to the corresponding stereoisomeric saccharic or tetra-hydroxy-adipic acids, $\text{COOH} \cdot (\text{CHOH})_4 \cdot \text{COOH}$. As would be expected, the ketoses on oxidation yield acids containing a smaller number of carbon atoms. The reducing properties of the monosaccharides are shown in their behaviour with ammoniacal silver nitrate solution, from which silver is precipitated, and particularly with Fehling's solution, from which on warming a reddish precipitate of cuprous oxide is thrown down. This behaviour is characteristic of ketoses as well as aldoses. In the absence of other reducing agents the last reaction may be employed not only for the qualitative detection of the monosaccharides, but also for their quantitative estimation. Schiff's reagent gives a red coloration with bioses and trioses, but not with the majority of pentoses and hexoses, presumably owing to the aldehydic group being masked by ring formation in the latter classes. A sensitised Schiff's reagent has been described² with which aldoses give a pink colour and may thereby be distinguished from ketoses.

The presence of a sugar can often be determined qualitatively by certain colour reactions. Among these may be mentioned the *formation*

¹ E. G. V. Percival *et al.*, *J.*, 1934, 1160; 1935, 648; 1936, 765. ² Tobie, *Ind. Eng. Chem. (Anal.)*, 1942, 24, 415.

of *furfural* (see index) by the action of aqueous hydrochloric acid upon pentoses. If a paper previously treated with aniline acetate is held in the escaping vapours, it develops a red coloration.

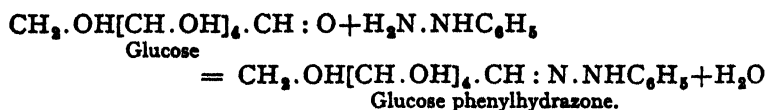
Molisch's test is also a general one. This consists in adding to the sugar solution one or two drops of a solution of α -naphthol, and pouring down the side of the vessel a little concentrated sulphuric acid (free from nitric acid). The furfural derivatives formed by the action of sulphuric acid produce a violet coloration at the junction of the two liquids, either in the cold or on gentle warming.

Some of the more important processes which have been devised for studying the relationships among the simpler carbohydrates are described in the following pages.

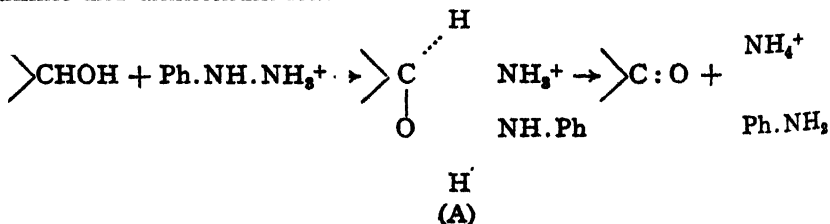
Osazones and the Conversion of Aldoses into Ketoses

As aldehydes or ketones the monosaccharides also react with hydrazines and hydroxylamine. *Phenylhydrazine*, $C_6H_5.NHNH_2$, has proved of the greatest value in the separation, identification and interconversion of the various monosaccharides. Without the aid of this reagent the brilliant researches of Fischer in the sugar group would hardly have been possible.

When 1 mol. of phenylhydrazine reacts with 1 mol. of an aldose or ketose, the first product is a normal hydrazone (see p. 189).

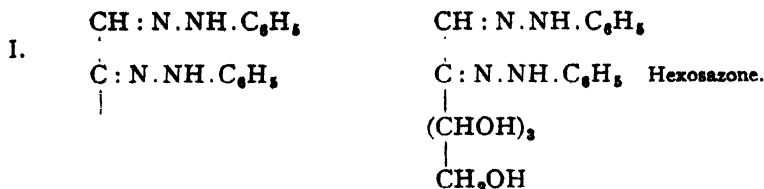


On warming with excess of phenylhydrazine, however, the hydrazone first formed is oxidised in such a way that the $CH.OH$ group adjacent to the original aldehydic or ketonic group is converted into a CO group¹. It is probable that this process is effected by the hydrazone ion, $C_6H_5.NH.NH_3^+$, since the reaction occurs under acid conditions.² The $CHOH$ group and the cation can be pictured as attaining the transition state (A). Dehydrogenation then occurs with simultaneous formation of aniline and ammonium ion.



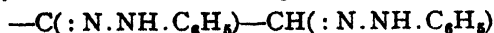
¹ In this reaction phenylhydrazine removes two atoms of hydrogen from the sugar and is converted into aniline and ammonia: $C_6H_5.NH.NH_2 + 2H = C_6H_5.NH_2 + NH_3$. E. A. Braude and W. F. Forbes, *J.*, 1951, 1762.

The CO group then combines with more phenylhydrazine to give a dihydrazone containing the group I. These compounds are termed **osazones**.



Prior to Fischer's researches one of the greatest barriers to a wider knowledge of the monosaccharides lay in the difficulty of separating mixtures of these sugars by crystallisation, owing to their high solubility in water and tendency to form syrups. The value of the osazones depends on the fact that they are sparingly soluble, and easily separable by crystallisation; and, in addition, from their melting-points and characteristic crystalline forms as seen under a microscope it is possible to identify the parent sugar.

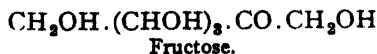
Osazones, like all hydrazones, are hydrolysed on being heated with hydrochloric acid, when phenylhydrazine is regenerated. The sugar originally employed, however, is not regained, as the group



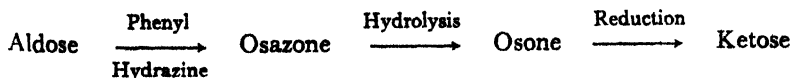
is converted into the group $-\text{CO}.\text{CHO}$. The highly reactive compound so formed is thus an oxidation product of the original sugar, and is termed an **osone**. In the example quoted above glucose yields



Osones may also be prepared by the action of benzaldehyde or *p*-nitrobenzaldehyde on the osazones. On mild reduction of this compound with zinc dust and dilute acetic acid the aldehydic group alone is attacked and converted into an alcoholic group, the keto group remaining unchanged. In this case, therefore, the sugar finally obtained is fructose, in place of the glucose used as starting material.



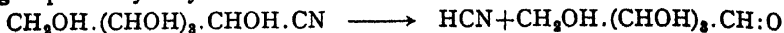
In these reactions we have a *general method of transforming an aldose into a ketose*, according to the scheme



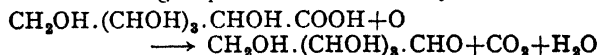
Descent and Ascent of the Aldose Series

Monosaccharides react with hydroxylamine to yield oximes, the aldehydic or ketonic oxygen being replaced by the group $:\text{N.OH}$. By use of these compounds Wohl (1893) devised a method of effecting the *degradation of an aldose to one of lower carbon content*. For example, glucose forms the oxime $\text{CH}_2\text{OH} . (\text{CHOH})_4 . \text{CH} : \text{NOH}$, which on being

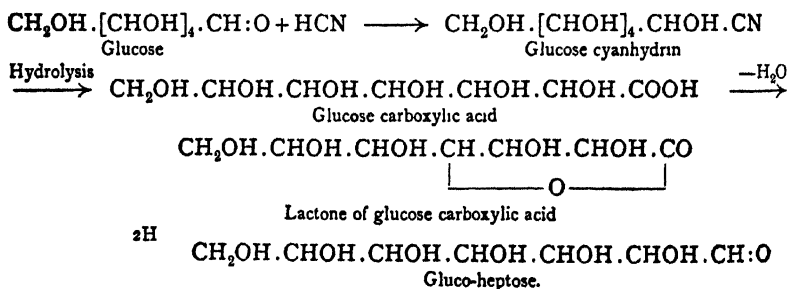
heated with acetic anhydride parts with water and is converted into the acetyl derivative of the nitrile $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CN}$. The latter on treatment with ammoniacal silver nitrate is decomposed, yielding hydrogen cyanide and the corresponding aldopentose, D-arabinose as the diaceta-mido compound which on hydrolysis yields the free sugar. The acetyl groups are hydrolysed at the same time.



Aldoses may also be degraded by Ruff's method by converting them into the corresponding monobasic acids, *e.g.* $\text{CH}_2\text{OH} \cdot (\text{CHOH})_4 \cdot \text{COOH}$, and oxidising the latter in the form of their calcium salts with hydrogen peroxide and a trace of a ferric salt (*Fenton's reagent*). In this reaction the carboxyl group is eliminated as carbon dioxide, and at the same time the adjacent alcoholic group is oxidised to aldehyde.



Monosaccharides, as aldehydes and ketones, also unite with hydrogen cyanide to form cyanhydrins. By use of this reaction, which is due to Kiliani (1886), we may effect the *synthesis of a higher from a lower aldose*. The cyanhydrins are first hydrolysed to hydroxy-acids, which are readily converted into lactones. The latter are then reduced to aldoses by means of sodium amalgam and dilute sulphuric acid. Glucose, $\text{C}_6\text{H}_{12}\text{O}_6$, under these conditions yields a new sugar, glucoheptose, $\text{C}_7\text{H}_{14}\text{O}_7$.



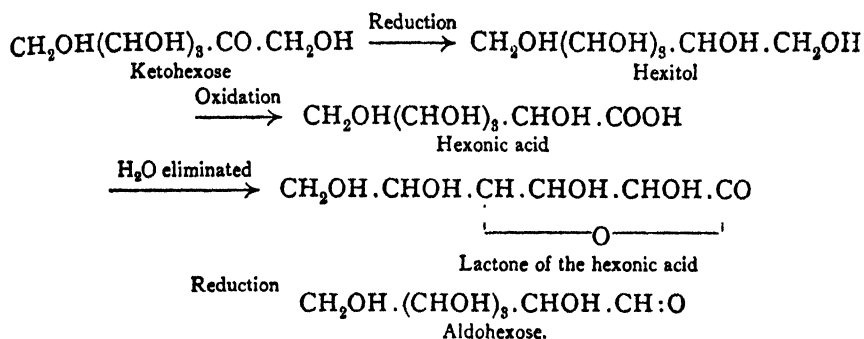
In a similar manner gluco-heptose may be used to build up an octose. The synthesis has been carried as far as a glucodecose.

It should be noted that, since a new asymmetric carbon atom is formed, two products should be isolated from a single aldose. In the early experiments of Kiliani (1886) only one product was isolated, but Fischer (1890) obtained both L-gluconic and L-mannonic acids from L-arabinose by the Kiliani synthesis (see also p. 302 for the addition of HCN to glycerose).

Conversion of Ketoses into Aldoses

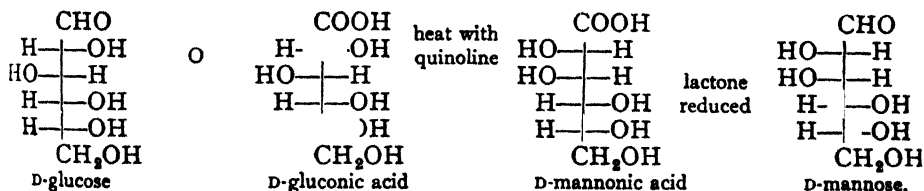
In this connection a series of reactions may be mentioned by means of which it is possible to pass from *ketoses into aldoses*. The ketose is

reduced to the corresponding alcohol, which on careful oxidation yields a mono-basic acid. This in turn readily passes into the lactone, from which an aldose is obtained by reduction with sodium amalgam in weakly acid solution, e.g.



Epimerisation

In synthetic work with the aldoses considerable use has been made of a process termed *epimerisation*,¹ which partially or completely reverses the configuration of the CHOH group in the α -position to the terminal aldehyde grouping (*cf.* p. 33). The aldose is first oxidised to the corresponding monocarboxylic acid, which is then heated with aqueous quinoline or pyridine, when the inversion of the α -group is more or less completely effected. On converting the new acid into the corresponding lactone, followed by reduction, a new aldose is obtained. This process may be illustrated by the transformation of glucose into mannose.



In this manner a number of new aldoses have been prepared.

Synthesis of Monosaccharides

Monosaccharides have been prepared artificially by the following methods :

1. Aldoses and ketoses may be formed quite generally by oxidation of the corresponding alcohols (for example, with nitric acid, sodium hypobromite, hydrogen peroxide and ferrous sulphate, or lead peroxide and hydrochloric acid). In this way arabinose, $\text{C}_5\text{H}_{10}\text{O}_5$, may be obtained from arabitol, $\text{C}_5\text{H}_{12}\text{O}_5$, and mannose from mannitol.

¹ *Epimers* (epimerides) are substances containing several asymmetric centres and differing only in the configuration of one of these.

By the conversion of DL-glucosazone isolated from α -acrose into DL-fructose via the osone followed by a series of reactions shown on p. 308, which included the resolution of DL-mannonic acid through its strychnine salts, epimerisation, etc. Emil Fischer (1890) successfully isolated D-fructose, D-glucose, D-mannose and their enantiomorphs as well as most of the other aldohexoses, thus achieving a virtual synthesis of these substances from their elements. The various steps in the synthesis have been dealt with previously in this chapter.

3. The formation of monosaccharides by the hydrolysis of polysaccharides and oligosaccharides with dilute acids has been mentioned on p. 300, *e.g.*,



4. Higher aldoses may be built up from lower members by the cyanhydrin method (see p. 306).

1. Bioses, Trioses and Tetroses

The simplest example of this group is glycollic aldehyde, $CH_2OH.CHO$, which can be obtained from glycol by oxidation with hydrogen peroxide, or from bromoacetaldehyde, $CH_2Br.CHO$, by treatment with baryta. It is a syrup of somewhat sweet taste. The two trioses, glyceric aldehyde and dihydroxy acetone, have already been mentioned (pp 301, 308). The former is prepared by oxidation of acrolein acetal and hydrolysis of the resulting acetal of glyceric aldehyde. It occurs in a stable dimolecular form, m.p. 138° , which in aqueous solution is slowly transformed into an enolic syrupy monomolecular form. *Dihydroxyacetone* is a crystalline compound, m.p. $68-75^\circ$, which is soluble in water and has a sweet taste. With sodium amalgam it is readily reduced to glycerol.

Glycollic aldehyde and glyceric aldehyde differ from higher aldoses in the ease with which they polymerise to compounds of twice their molecular weight. In other ways also the aldehydic character is more pronounced than with the higher sugars. Among the tetroses, DL-erythrose is obtained by oxidation of the corresponding alcohol *i*-erythritol, and by the condensation of glycollic aldehyde. In the former case the product consists mainly of a mixture of aldotetrose and ketotetrose; in the latter case the aldotetrose is probably formed.

Additional methods of preparing tetroses include the *degradation of pentoses* by way of the oximes (see p. 305), and the *oxidation of pentonic acids* (in the form of their calcium salts) with hydrogen peroxide in the presence of a trace of ferric salt (p. 306).

2. Pentoses

Aldopentoses of the formula



contain three asymmetric carbon atoms, and according to theory should therefore exist in eight optically active and four racemic forms. Two of these, *L-arabinose* and *D-xylose*, occur in the combined state in the vegetable kingdom in the complex polysaccharides *pentosans*, and in the form of glycosides: *D-arabinose* occurs to a smaller extent in aloin

and the lipoids of tubercle bacilli, and *D-ribose* is found as a constituent of the nucleoproteins (p. 812). These naturally occurring sugars are described below. Other pentoses have been prepared synthetically.

In their chemical behaviour pentoses possess the general properties of the monosaccharides, but in addition give characteristic reactions by which they are easily recognised and distinguished from hexoses. For example, when heated with diluted hydrochloric or sulphuric acid they yield *furfural*, $C_5H_4O_2$ (methyl pentoses give methylfurfural), which forms sparingly soluble derivatives with phloroglucinol. This reaction is used in the quantitative estimation of pentoses. A qualitative test for pentoses consists in heating them with *hydrochloric acid and phloroglucinol*, when a cherry-red coloration is produced.

The pentoses do not undergo fermentation.

L-Arabinose,¹ is obtained together with xylose by boiling gum arabic, cherry gum, or the pith of maize and elder with dilute sulphuric acid (hydrolysis of pentosans). It forms prisms, m.p. 160° , and is dextrorotatory. On reduction it yields *L-arabitol*, and on oxidation passes first into *L-arabonic acid* $CH_2OH.(CHOH)_3.COOH$, and finally into *L-arabo trihydroxy-glutaric acid*, $COOH.(CHOH)_3.COOH$.

D-Arabinose, the optical antipode of the above compound, is produced by the degradation of D-glucose-oxime or of D-gluconic acid. **DL-Arabinose**, m.p. 164° , is formed by combination of the two optically active components and is possibly the pentose which is present in human urine in cases of pentosuria.

D-Xylose, or wood sugar, can be obtained from a variety of vegetable

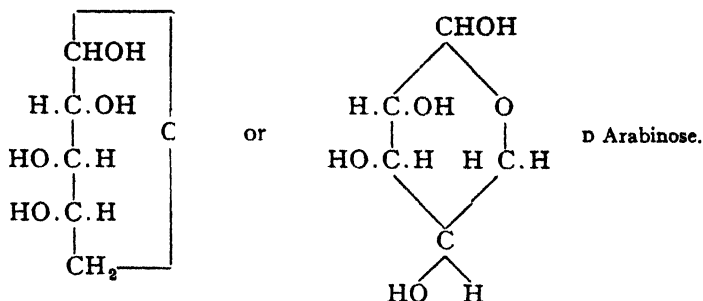
products, *e.g.* by boiling bran, maize cobs, wood or straw with dilute acids. It is dextro-rotatory, and on reduction yields *i*-xylitol. When oxidised it gives first D-xylonic acid and finally *i*-trihydroxy-glutaric acid. **D-Xylose** is also formed by the degradation of D-gulonic acid, and by synthetic methods may be converted into D-gulose. When degraded through the oxime it yields D-threose which is oxidisable to (–)-tartaric acid. These reactions lead to the above configuration for D-xylose.

D-Ribose is present in certain nucleic acids (p. 374). It forms the same osazone as D-arabinose gives an inactive trihydroxyglutaric acid on oxidation and therefore has the configuration given.

Arabinose and xylose exhibit mutarotation (see p. 82), *i.e.*, the rotation of a freshly prepared solution changes with time until a constant value is attained. In both these cases the rotation diminishes. An explanation of this peculiarity is given on p. 312.

¹ For further information concerning the methods by which the configurations of the pentoses and hexoses have been derived see C. S. Hudson, *J. Chem. Ed.*, 1941, 18, 353.

For simplicity of presentation the pentoses have been represented in the foregoing pages as open-chain sugars. The work of Haworth, however, leaves no doubt that they actually exist in cyclic structures of



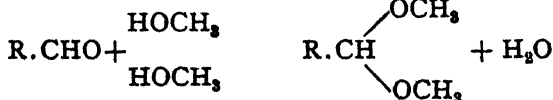
the ether type containing a 6-membered ring (see p. 316). L-Arabinose is therefore more correctly formulated by either of the above structures, in which, as before, a CHOH group of the D-configuration is written with the OH to the right.

3. The Hexoses and Glycosides

Cyclic Structure of Monosaccharides

Hexoses are compounds of sweet taste, which are generally difficult to obtain in the crystalline state. They are very soluble in water, sparingly soluble in absolute alcohol, and insoluble in ether. The study of this group provided an admirable opportunity of putting stereochemical theory to an exacting test, from which it has emerged unscathed.

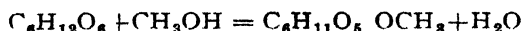
The **aldohexoses**, $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CH}:\text{O}$, contain four asymmetric atoms, and according to theory should exist in sixteen optically active isomerides, consisting of eight pairs of enantiomorphs. All of these compounds are known, and their configurational formulæ are given on p. 317. It is now known, however, that the monosaccharides are not open-chain aldehydes and ketones, but cyclic compounds having an ether structure. Such a structure, it may be remarked, was suggested by Tollens as long ago as 1883, but was not generally accepted until many years later. The evidence upon which cyclic structures have been assigned may be illustrated by considering D-glucose. Glucose gives a positive test only with a specially prepared Schiff's solution. Moreover while a normal aldehyde reacts with methanol and hydrogen chloride to give an acetal, D-glucose reacts with one molecule only to give a mixture of hemiacetals termed methylglucosides (see below).



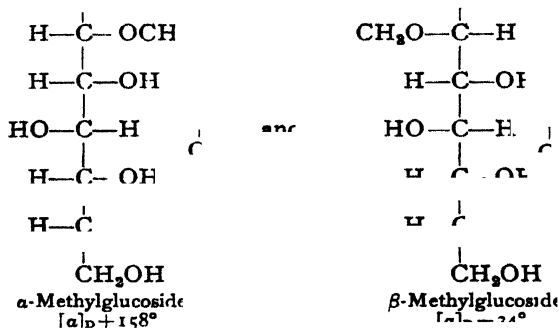
It is therefore clear that the aldehydic group in glucose is modified or masked in some way and lacks pronounced aldehydic characteristics.

The full significance of this was appreciated only when the problem was attacked from other standpoints, including particularly the study of the glycosides and the researches on methylated sugars initiated many years ago by Purdie and developed with conspicuous success by Irvine, Haworth and Hirst.

A hexose such as glucose combines with methyl alcohol in the presence of hydrogen chloride to form a mixture of two stereoisomeric methyl glycosides.¹ These compounds do not react with phenylhydrazine and hence contain no free aldehyde group. Although comparatively stable



towards alkalis, they are readily hydrolysed by hot dilute acids. If 1



evident therefore that the aldehyde group is now united to alcohol in the same manner as in the acetals (see p. 188). But since only one molecule of alcohol enters into combination with a molecule of glucose, with loss of one molecule of water, it must be assumed that an alcoholic group of the sugar also takes part in the process, to form a cyclic anhydride.

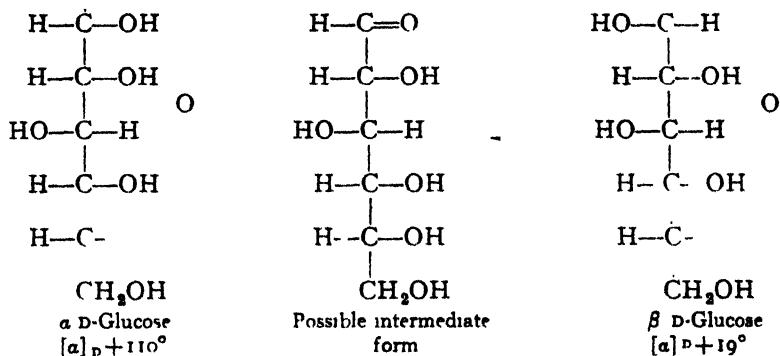
It will be seen that the end carbon atom (1) has now become asymmetric and can thus exist in either the D- or L-configuration. There will therefore be two stereoisomeric glucosides, which are distinguished as the α - and β -forms. The actual hydroxyl group engaged in ring-formation was extremely difficult to identify with certainty, and at first it was assumed, by analogy with the lactones of γ -hydroxy acids, that the union was to the C-atom in position 4. A cyclic structure of this kind is described as containing a butylene oxide or 1:4-oxidic ring. Later research has shown that these compounds actually contain a 1:5- or amylenic oxide ring as illustrated in the above formulæ.

The behaviour of glucose in undergoing mutarotation—discovered by Dubrunfaut in 1846—led to the suggestion that the free sugar also occurred in cyclic forms corresponding to the α - and β -glucosides, and

¹ E. Fischer, *Ber.*, 1893, 26, 2400. Compounds of this type are now described under the general heading of glycosides. Each individual product is named after the particular sugar present, e.g. glucosides from glucose, fructosides from fructose and maltosides from maltose (see p. 322).

that mutarotation was due to the partial conversion of one form into the other through an intermediate open-chain glucose. Tanret (1895) had isolated two forms of D-glucose, one, α -D-glucose showing a change of rotation in solution of $+110^\circ \rightarrow +52.5^\circ$, whilst the other, β -D-glucose, changed from $+19^\circ$ to the same equilibrium value. Simon suggested that these crystalline isomeric glucoses were probably analogous to the α - and β -methylglucosides of Fischer.

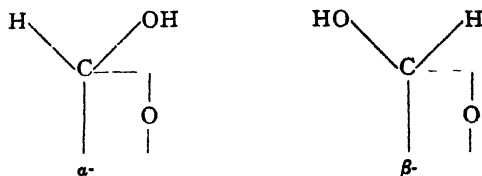
Definite proof of this was obtained by E. F. Armstrong. In common with other α - and β -glucosides the methyl glucosides show characteristic differences in their behaviour towards certain hydrolytic enzymes. *Maltase*, an enzyme which is present in yeast and various other sources, rapidly hydrolyses α -methyl glucoside in aqueous solution to methyl alcohol and glucose, but has no influence on the β -glucoside. On the other hand, the latter is readily hydrolysed by the enzyme *emulsin*, which is present in bitter almonds. Emulsin, however, does not attack the α -compound. By this means glucosides have been



classified as α - and β -glucosides, according to their behaviour towards these enzymes. Armstrong demonstrated that two glucoses of different rotatory powers were formed when α - and β -methyl glucosides respectively were hydrolysed by enzymes. The glucose liberated from the α -glucoside had a high rotation and was therefore α -glucose, whereas the glucose from the β -glucoside had a very low rotation and was clearly β -glucose. In a short time, or more rapidly on addition of ammonia, each of the newly liberated forms changes into the same equilibrium mixture of α - and β -glucoses having a rotation of intermediate value.

It is clear that with the introduction of a new asymmetric carbon atom on C_1 every sugar which exists in a cyclic form will give rise to a pair of α - and β -isomers, so that the number of D-aldohexoses is increased to sixteen. It will be noted, of course, that the α - and β -D-glucose (to take an example) are not enantiomorphs since the asymmetry on C_1 only is involved. The existence of such isomeric pairs is not confined to sugars, but occurs in the case of derivatives such as glycosides, as we have seen, acetates, halogen derivatives, and many others.

C. S. Hudson (1909) suggested a convention for recognising and representing the configurations of α - and β -forms of sugars and their derivatives. In the D-series the isomer with the highest positive rotation is called α , and written with the hydroxyl group on the right, and the isomer with the low rotation in the D-series is called β , and represented with the hydroxyl group on C₁ to the left.



The reverse holds in the L-series, the enantiomorph of α -D-glucose being α -L-glucose.

It will be noted that the hydroxyl groups on C₁ and C₂ in α -D-glucose are *cis*, and in the β -form *trans*. Böeseken (1913) found experimental support for this by measuring the electrical conductivity of boric acid solutions containing freshly dissolved α -D-glucose and β -D-glucose respectively. In the former case the conductivity was found to fall from a high initial value to an equilibrium value parallel to the mutarotation whilst in the case of β -glucose the conductivity rose almost to the same value. This effect is ascribed to complex formation between the boric acid and the *cis*-glycol grouping present in α -D-glucose. More recently it has been shown that the conductivity of a boric acid solution of 3 : 4 : 6-trimethyl α -D-mannose rose with the mutarotation.¹ In this case the hydroxyl groups on C₁ and C₂ are *trans* in the α - and *cis*- in the β -form and this latter form is, of course, present in the aqueous solution at equilibrium. In this particular example the only free hydroxyl groups were those whose configuration it was decided to investigate.

In 1914 Emil Fischer² discovered a third form of methylglucoside, which he described as a γ -form in order to distinguish it from the previously known α - and β - varieties. A year later Irvine isolated a tetramethyl γ -glucose (*i.e.* a γ -glucose having four OH groups replaced by OCH₃) which was extremely reactive. Irvine also showed that Fischer's γ -glucoside was a mixture of two stereoisomeric forms (*cf.* α - and β -methyl glucosides), but found that the corresponding γ -glucose was too labile to be isolated. Owing to its unstable nature the γ -glucose grouping in these compounds was formulated as possessing a different type of ring structure from that present in the crystalline α - and β -glucoses and glucosides.

Later research by Haworth and his co-workers on methylated monosaccharides and lactones of hydroxy acids (see below) has shown that the ordinary *pentoses and hexoses normally exist in the 1:5- or amylene oxide form* and that the *labile γ -sugars possess a 1:4- or butylene oxide ring*. These conclusions are based upon the following lines of argument :

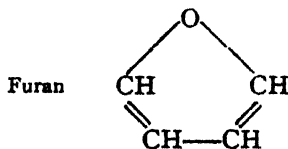
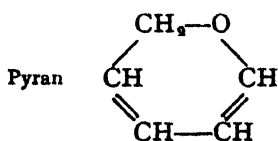
¹ H. T. Macpherson and E. G. V. Percival. *J.*, 1927, 1020.

² *Ber.*, 1914, 47, 1980

(1) a study of the relationships existing between the rotatory powers of the various methylated and unmethylated sugars, (2) the conversion of the monosaccharides into their completely methylated forms, followed by an investigation of the products given by the latter on oxidation, and (3) a study of the rates with which the lactones of the series are hydrolysed to form the open-chain acids. Haworth has shown that among the lactones of the carboxylic acids, the δ -lactones as a class are much more rapidly hydrolysed in water than the γ -lactones.

As an example of Haworth's methods we may quote the case of glucose. The α - and β -methyl glucosides I (prepared from glucose) were methylated and then hydrolysed to give the normal crystalline tetramethyl glucose II and this on mild oxidation was converted into the corresponding lactone IV, which from its rate of hydrolysis was characterised as a δ -lactone having the oxygen bridge in the 1:5-position. A similar amylene oxide structure may be assumed for the original sugar, since Armstrong had related the crystalline methylglucosides to the α - and β -glucoses. Further confirmation of the correctness of these deductions is obtained by the oxidation of the lactone IV to xylotrimethoxyglutaric acid V by means of concentrated nitric acid. (For formulæ I-V, see next page.) Similar methods have been applied to other aldoses and ketoses.

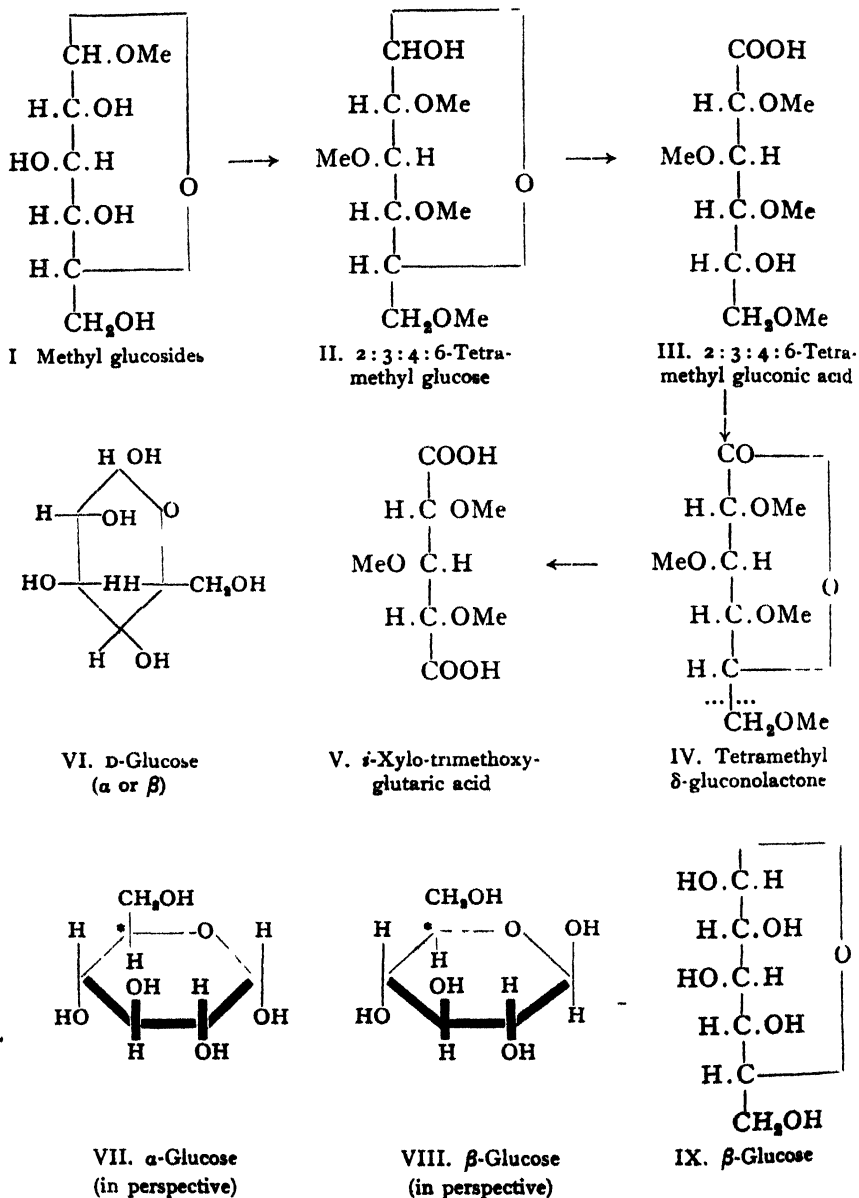
Haworth has shown that the properties of the monosaccharides are best represented by regarding them as derivatives of the cyclic compounds *pyran* and *furan*. Thus the monosaccharides which normally occur with an amylene oxide ring are now described as belonging to the **pyranose type**, e.g. *glucopyranose* (see formulæ VI and VII, p. 316). On the other hand, the labile γ -sugars are of the **furanose type**, examples of this class being the above-mentioned tetramethyl glucofuranose (tetramethyl γ -glucose) and fructose, which exists as fructopyranose in the



free state but occurs as fructofuranose in derivatives such as cane sugar (p. 325) and inulin (p. 330). These formulæ also illustrate the ease with which the side-chain (CH_2OH) in glucose is oxidised to the carboxyl group, yielding glucuronic acid.

In formulæ such as VI the usual convention holds as to the disposition of the CHOH groups, a D-configuration being written with H on the left-hand side. When these conventional formulæ are built up in model form, the necessity of bringing the bond joining C_5 (marked by *) to O into the same plane as the other C-atoms of the ring is found to cause an apparent displacement of the groups around C_5 (VII and VIII).

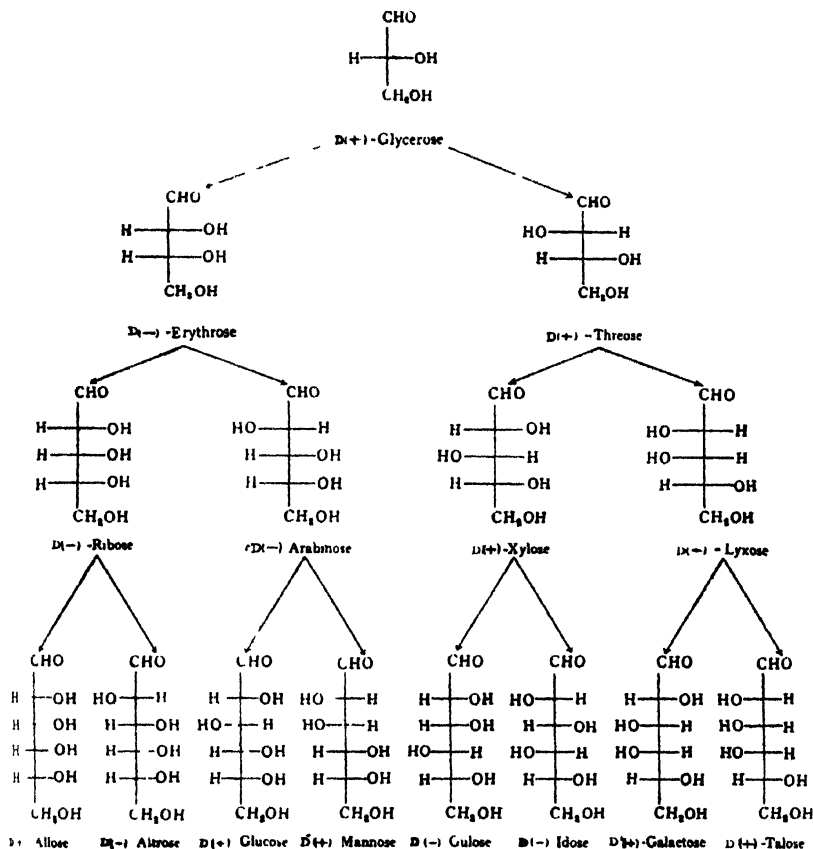
This change is readily observed on converting the open-chain aldehydic model into the ring structure. It may be added that the X-ray measurements made by E. G. Cox and his co-workers¹ on a number of sugars



and sugar derivatives have substantiated the allocation of pyranose and furanose structures by purely chemical methods.

¹ E. G. Cox, T. H. Goodwin, and A. E. Wagstaff, *J.*, 1935, 1495.

D-Series of the Aldoses



$(\text{CH}_3)_2\text{C}:$, each linked to two oxygen atoms of glucose. These *isopropylidene derivatives* are readily hydrolysed by mineral acids, but not by alkalis.

A test for ketoses is the evanescent red coloration formed when they are heated with resorcinol and $12\frac{1}{2}$ per cent. hydrochloric acid (*Seliwanoff test*).

An outstanding property of certain hexoses is their ability to undergo fermentation. As has been shown by E. Fischer, this property is intimately connected with the spatial configuration of the sugar.

(a) *Aldohexoses*, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CHO}$

D-Glucose, *grape sugar*, *dextrose*, melts in the anhydrous state at 146° , the hydrated form (H_2O) melting at 86° . It is found together with fructose in grapes, figs, and other sweet fruit, and also in honey. In small quantities it occurs in certain animal products, *e.g.* the urine of diabetic patients. Glucose and fructose are the only hexoses which occur in the free state.

Glucose is also formed by the hydrolysis of the polysaccharides, cane sugar, starch, and cellulose, and is prepared industrially from starch by boiling it with dilute sulphuric acid. The commercial glucose so obtained is largely used in the manufacture of sweets and in the wine industry.

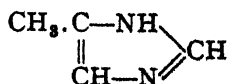
The synthesis of D-glucose by E. Fischer has already been discussed (p. 308).

α -Glucose ($[\alpha]_D + 110^\circ$) may be prepared by allowing glucose to crystallise at ordinary temperatures from acetic acid containing a little water. Crystallisation from pyridine or at higher temperatures from pure acetic acid yields **β -glucose** ($[\alpha]_D + 19^\circ$). Ordinary glucose chiefly the α -compound.

Glucose undergoes the general reactions of aldoses described above. On oxidation it first yields *D-gluconic acid*, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{COOH}$, and finally *D-saccharic acid*, $\text{COOH}(\text{CHOH})_4\text{COOH}$. On reduction it is transformed into the hexahydric alcohol, *D-sorbitol*, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CH}_2\text{OH}$. It has already been mentioned that grape sugar is readily fermented, the main products of the action being alcohol and carbon dioxide.

Under the influence of dilute alkalis it suffers a series of changes and decompositions, which lead to the formation of hydroxy acids, such as lactic acid. On electrolytic oxidation at a lead anode it breaks up into formaldehyde and a pentose.

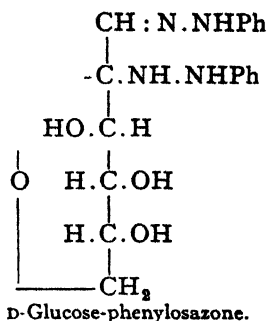
When treated with ammonia in the form of ammoniacal zinc hydroxide, glucose is converted, even at the ordinary temperature, into methyl-*iminazole* (methylglyoxaline).



D-Glucose-phenylosazone is an intermediate in the conversion of D-glucose into D-fructose (see p. 305). It is sparingly soluble in water, from which it crystallises in yellow needles, m.p. 204° to 205° .

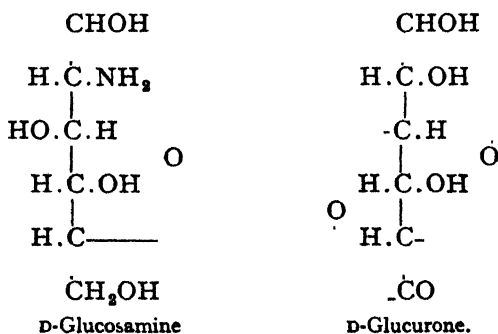
Glucosazone, like galactosazone, is known to undergo mutarotation in solution. It is claimed¹ that this is due to the presence of a 2 : 6-oxide ring in each of the above osazone structures.

D - Glucosamine, *chitosamine*, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_3 \cdot \text{CHNH}_2 \cdot \text{CHO}$, is of special interest, as it stands midway between glucose and the α -amino acids, and thus forms a link between the carbohydrates and the proteins. It was first prepared from lobster shell by boiling the polysaccharide chitin contained therein with hydrochloric acid. Glucosamine and other hexosamines are formed from mucins, the constituents of animal mucus, and from other proteins by hydrolysis with acids. The relationship of glucosamine to grape sugar is shown by its conversion into phenylglucosazone on treatment with phenylhydrazine.



D-Glucosamine was synthesised by Fischer and Leuchs in the following manner: D-arabinose, by treatment with ammonia, was converted into D-arabinosimine, which with hydrogen cyanide gave D-glucosaminic acid, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_3 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$. The lactone of this acid was then reduced to D-glucosamine by means of sodium amalgam.

It has now been shown² that glucosamine is stereochemically related to glucose and not to mannose, a point in doubt which is not settled by the synthesis of Fischer and Leuchs. Furthermore, glucosamine has a pyranose structure



D-Glucuronic acid, $\text{HOOC} \cdot (\text{CHOH})_4 \cdot \text{CHO}$, is obtained by reducing the lactone of saccharic acid, $\text{HOOC} \cdot (\text{CHOH})_4 \cdot \text{COOH}$. It occurs in urine, either united with phenols in compounds of an ether type or with aromatic carboxy acids in the form of esters. In this way the phenols

¹ E. E. Percival and E. G. V. Percival, *J.*, 1935, 1398; E. G. V. Percival *et al.*, *ibid.*, 1936, 1770; 1937, 1320; 1938, 1384; 1940, 1479; 1941, 750. ² W. N. Haworth, W. H. G. Lake, and S. Peat, *J.*, 1939, 271.

resulting, for example, from intestinal putrefaction are rendered harmless to the body. This protective function of glucuronic acid is also exerted by sulphuric acid and glyccoll. Glucuronic acid does not crystallise readily, and in this respect differs from its lactone, glucurone.¹

D-Mannose is produced by careful oxidation of the hexahydric alcohol mannitol, which is present in various plants, or by boiling the polysaccharide seminine, occurring in the shell of the ivory nut, with dilute sulphuric acid. Synthetically, it is obtained by reducing D-mannonic acid with sodium amalgam. It is a white hygroscopic compound of lower rotatory power than D-glucose, from which it differs only in the relative arrangement of the groups attached to the carbon atom adjacent to the aldehyde group (see p. 317). From this it follows that D-mannose and D-glucose yield the same osazone.

Oxidation converts D-mannose first into *D-mannonic acid*, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{COOH}$, and then into *D-mannosaccharic acid*, $\text{COOH}(\text{CHOH})_4\text{COOH}$. It can be fermented with yeast.

The conversion of D-mannose into D-glucose may be effected through the intermediate formation of D-mannonic acid.

D-Galactose is formed together with D-glucose by the hydrolysis of milk sugar, and also of *galactitol*, $\text{C}_6\text{H}_{14}\text{O}_7$, a substance present in the yellow lupin. It melts at 168° , is dextrorotatory, exhibits mutarotation and may be fermented. On reduction it yields *i-dulcitol* (p. 268), and on oxidation gives first *galactonic acid*, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{COOH}$, and then *mucic acid*, $\text{COOH}(\text{CHOH})_4\text{COOH}$, which is a meso form.

(b) *Ketohexoses*, $\text{CH}_2\text{OH}(\text{CHOH})_3\text{CO}\cdot\text{CH}_2\text{OH}$

$ \begin{array}{c} \text{CH}_2\text{OH} \\ \\ -\text{C}\cdot\text{OH} \\ \\ \text{HO}\cdot\text{C}\cdot\text{H} \\ \\ \text{H}\cdot\text{C}\cdot\text{OH} \\ \\ \text{H}\cdot\text{C}\cdot\text{OH} \\ \\ -\text{CH}_2 \end{array} $	<p>D-Fructose, <i>fructopyranose</i>, also known as fruit sugar or <i>lævulose</i>, melts at 95° and is found with D-glucose in honey and the juice of sweet fruits. The hydrolysis of cane sugar leads to the production of equimolecular amounts of D-fructose and D-glucose. On the other hand, inulin, a polysaccharide occurring in the roots of the dahlia, chicory and many <i>Compositae</i>, yields D-fructose alone. From the latter sources it is prepared industrially.</p>
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D-Fructopyranose.

The osazone of fructose is formed very readily, even in the cold, and is identical with D-glucosazone (compare configurational formulæ of fructose and glucose). The conversion of glucose into fructose by way of the osazone has already been described on p. 305. In consequence of its spatial relationship to D-glucose fruit sugar is known as D-fructose, although it has a laevorotation of $[\alpha]_D = -92^\circ$. As represented above, fructose normally exists in the form of fructopyranose, with a 1:5-oxidic ring. In the combined state, however, the fructose residue contains a 1:4-ring and is thus of the fructofuranose type (see cane sugar).

¹ F. Smith, *J.*, 1944, 584.

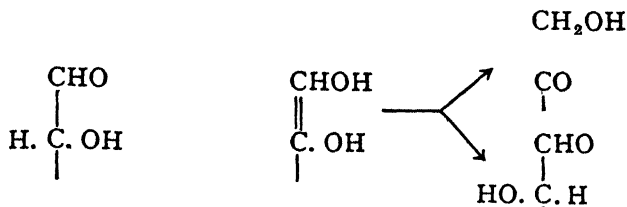
Fructose is more soluble in water than glucose, is more difficult to crystallise, and is readily fermented, when it gives the same products as grape sugar. On reduction it is converted into a mixture of D-mannitol and D-sorbitol. On oxidation it breaks up into D-erythronic acid, $\text{CH}_2\text{OH}(\text{CHOH})_2\text{COOH}$, and glycollic acid, $\text{CH}_2\text{OH}\cdot\text{COOH}$.

*Interconversion of D-Glucose, D-Fructose and D-Mannose*¹

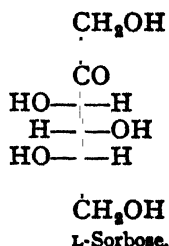
As was first shown by Lobry de Bruyn, any one of the above three hexoses, under the influence of hydroxyl ions (very dilute alkalis or alkaline earths, sodium acetate, ammonia, etc.), is converted into a mixture of all three sugars in equilibrium with one another, as indicated in the following scheme :



Enolic forms appear to act as intermediates in the above changes, the simplest conception due to Lewis² being given below :



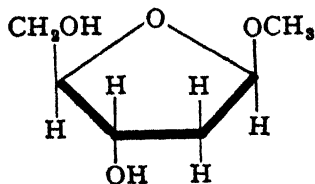
L-Sorbose, *sorbinose*, m.p. 154° , is a ketose obtained from the juice of mountain-ash berries. These contain the alcohol D-sorbitol, which is converted into sorbose by the action of an oxidising organism, *Bacterium xylinum*. L-Sorbose is now produced in quantity from the sorbitol prepared by catalytic hydrogenation of D-glucose for the synthesis of ascorbic acid. It is not fermented by yeast.



Deoxy Sugars

As the name implies, these compounds contain less oxygen than the pentoses and hexoses from which they are derived.

2-Deoxyribose, also called 2-*Ribodesose*, is the characteristic sugar of thymus nucleic acid, in which it occurs in the furanose form.

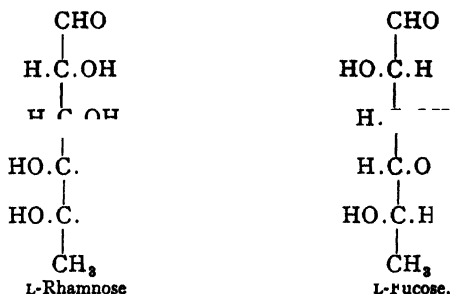


β -Methyl 2-deoxy-D-ribofuranoside.

¹ Lobry de Bruyn and A. van Ekenstein, *Ber.*, 1895, 28, 3078. Lewis, *J.A.C.S.*, 1932, 54, 1040.

² D. J. Loder and W. L.

Methylpentoses or 6-Deoxyhexoses.—Of this group L-rhamnose or 6-deoxy-L-mannose and L(–)-fucose (6-deoxy-L-galactose) are important.



L-Rhamnose occurs in many glycosides and L-fucose is a constituent of sea-weed polysaccharides (*e.g.* fucoidin). D-isoRhamnose (6-desoxy-D-glucose) occurs naturally in the glycoside *convolvulin* and was the first member of this group to be synthesised (E. Fischer and L. Zach, 1912).

The nomenclature of this group has been simplified by using the general suffix methylose; thus rhamnose may be named L-mannomethylose, and *isorhamnose* D-glucomethylose.

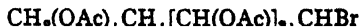
Glycosides

In close relationship to the monosaccharides are the glycosides, which are found very widely distributed in the vegetable kingdom. They may be considered as derivatives of the ether type formed by combination of a sugar (commonly glucose) with one or more other substances. Well-known representatives of this class are *amygdalin*, a constituent of bitter almonds; *salicin*, which was used as a febrifuge by the older school of medicine; *indican*; *ruberythric acid*. *Linamarin*, the glucoside of *acetone-cyanhydrin*, $\text{C}_6\text{H}_{11}\text{O}_5 \cdot \text{O} \cdot \text{C}(\text{CH}_3)_2 \cdot \text{CN}$, was first isolated from the seeds and embryo of flax. Under the influence of enzymes, or on being heated with dilute acids or alkalis, a glycoside breaks down into a sugar (or mixture of sugars) and the compound with which it was originally united. The sugar-free compound is known as an *aglucone* or *aglycone*.

Glycosides of the simplest type have been synthesised by E. Fischer, by bringing a sugar, *e.g.* glucose, into reaction with an alcohol in the presence of hydrochloric acid.



Another compound, introduced by Koenigs and Knorr, of great value in the synthesis of glycosides and other sugar derivatives, is *aceto-bromo-glucose*, prepared from penta-acetyl-glucose by treatment with hydrobromic acid.



As is shown by the inactivity of these compounds towards phenylhydrazine, they no longer contain a free aldehyde group. The latter must therefore be united to the alcohol in the same manner as in the acetals (see p. 188). For the isomerism of α - and β -glucosides and a means of distinguishing between these two forms by enzyme action, see p. 313 *et seq.*

A detailed investigation of the simpler artificial glycosides led Fischer to the discovery that there was no fundamental difference between the glycosides and the polysaccharides. The latter are glycosides of the monosaccharides themselves.

II.—DISACCHARIDES, $C_{12}H_{22}O_{11}$

Unlike the polysaccharides, the di- and trisaccharides still retain the sweetness of taste characteristic of monosaccharides.

Until recently the only disaccharides known were derived from the hexoses, $C_6H_{12}O_6$, and therefore possessed the formula $C_{12}H_{22}O_{11}$. On hydrolysis these take up water and are decomposed into two hexose molecules, $C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$. This change may be effected by boiling with dilute acids, or by the action of enzymes such as diastase, emulsin and invertase. All disaccharides yield glucose as one of the hydrolytic products, the other may also be glucose (as in the case of maltose), fructose (from cane sugar), or galactose (from milk sugar).

Disaccharides have been found in plants which give on hydrolysis 1 mol. hexose and 1 mol. pentose, *e.g.* *vicianose* (Bertrand) an arabinosido-glucose, and *primverose*, a xylosido-glucose. Both of these disaccharides have been synthesised by Helferich.¹

The ease with which disaccharides are hydrolysed supports the view that they are glycosides. If union occurs in such a way that the reducing group of one of the hexose constituents is left intact, then the disaccharides so formed (*e.g.* lactose and maltose) will still exhibit the reactions of aldoses. They will reduce Fehling's solution and give osazones with phenylhydrazine. On the other hand, cane sugar shows none of these reactions, and in it the reducing groups of both glucose and fructose are combined.

In determining the constitution of di- and poly-saccharides it is necessary to determine (1) the nature of each ring present, (2) the point of junction between the sugar residues, and (3) the nature of the glycosidic group involved. The chief difficulty lies in deciding the exact position of the oxygen linkings taking part in the junction of the simple sugar units and the particular stereo-isomeric forms of the monosaccharides present. Some information on these points is afforded by a study of enzyme action.

¹ B. Helferich and co-workers, *Ann.*, 1927, 455, 168; 1928, 465, 166. *Some Constitutional Problems of Carbohydrate Chemistry*, Irvine, J., 1922, 123, 898; *The Constitution of Sugars*, W. N. Haworth.

In recent years this problem has been attacked systematically on lines initiated by Purdie and Irvine and developed by W. N. Haworth and his school as the result of the application of the methyl sulphate process of methylation. The method adopted involves, in the first instance, the preparation of a large number of partially or completely methylated aldoses and ketoses as reference compounds. The disaccharide or polysaccharide under investigation is then fully methylated¹ and submitted to careful hydrolysis followed by other chemical changes, *e.g.* oxidation. From an examination of the simpler methylated derivatives so obtained it is possible to determine the structure of the parent compound.

Cane Sugar, sucrose, saccharose, occurs in the juice of the sugar cane, sugar beet, sugar maple, maize, and many other plants. The first two sources in particular are utilised in the preparation of sugar on the large scale.

Technical Preparation of Sugar from Beets.—The beets are sliced into thin sections by mechanical means, and the sugar is extracted by a *diffusion process* involving systematic treatment with water. The water is first admitted to a “diffuser” containing the almost completely extracted roots, and after remaining there for a few minutes is transferred to the next in the series, finally coming into contact with fresh roots. The extracted roots are expressed and utilised as fodder, after being dried to keep them in good condition.

The subsequent *processes for purifying the juice* have as their aim the removal of the majority of other organic substances present, which would otherwise hinder the crystallisation of the sugar. For this purpose the extract is treated at a moderate temperature with milk of lime, by which means oxalic acid, citric acid, and phosphates are precipitated, other acids are neutralised or, like asparagine, decomposed, and most of the protein and colouring matter is thrown out of solution. The necessity of using an excess of lime leads to the formation of insoluble calcium sucrate; this is decomposed by passing in carbon dioxide, when calcium is precipitated as calcium carbonate. Sulphur dioxide is frequently used in place of carbon dioxide, and yields an extract of better colour.

In order to avoid decomposition the *evaporation of the purified extract* is conducted in vacuum pans, and is continued until a concentration is reached at which crystallisation sets in. Finally, the masses of crystals are broken up and the mother liquor removed by centrifuging. The moist crystals remaining in the centrifuge constitute the *raw sugar* of commerce, and the dark brown fluid which is run off is known as *molasses*.

Raw sugar is refined by bringing it into solution, treating with milk of lime, and filtering through “activated” charcoal. After several repetitions of this process the liquid is concentrated in vacuum pans until crystallisation sets in. The refined sugar so obtained contains 99.9 per cent. sucrose. Sugar refining is also effected by ion exchange which removes salts and yields a sugar juice containing 96-98 per cent. sugar.

Recovery of Molasses.—Molasses contains about 20 per cent. water and 50 per cent. sugar. The latter, however, is only in part recoverable by further concentration of the molasses, as it is held in solution by the presence of impurities. It is therefore necessary to separate the sugar from the residual matter by special treatment, for which purpose a large number of processes are available, *e.g.* separation by means of *strontium* or *calcium* *sucrates*. This process depends on the property which sugar possesses of giving insoluble or sparingly soluble sucates with lime or strontium hydroxide, *e.g.* *tricalcium sucate*, $C_{12}H_{22}O_{11}$, $3CaO$, *distrontium sucate*, $C_{12}H_{22}O_{11}$, $2SrO$. When the diluted molasses is treated with either of the above hydroxides a precipitate of the

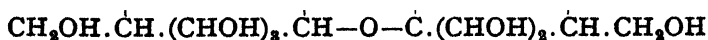
¹ W. N. Haworth, *J.*, 1915, 107, 8.

corresponding sucrate is thrown out of solution. Inorganic and organic impurities in the molasses remain dissolved and are removed in a filter press. After washing the sucrates with a little water or aqueous alcohol they are decomposed with carbon dioxide, and the sugar solution so obtained is evaporated as before in vacuum pans.

Properties of Cane Sugar.—Cane sugar crystallises in clear monoclinic prisms, which are very sparingly soluble in alcohol, but dissolve easily in water to give a solution rotating the plane of polarisation to the right. Cane sugar melts at 160° and on cooling solidifies to a vitreous mass (*barley sugar*), which gradually reverts to the crystalline state. On stronger heating it forms a brown product known as *caramel*, a mixture of decomposition products of sugar used for tinting liqueurs and confectionery. As has already been mentioned above, it forms sucrates with bases. When warmed with dilute acids it is rapidly hydrolysed to a mixture of glucose and fructose. Glucose resembles cane sugar in being a dextrorotatory compound, but fructose is so strongly laevorotatory that the equimolecular mixture of glucose and fructose obtained by hydrolysis rotates the plane of polarisation to the left. For this reason the above process is known as the *inversion of cane sugar*, and the mixture of D-glucose and D-fructose so obtained is called *invert sugar*. The latter usually forms a syrup, which is sweeter than cane sugar and is used as a substitute for honey, for improving wine musts, and in the preparation of champagne, liqueurs and fruit preserves.

Structure of Sucrose

Cane sugar no longer gives the reactions of the monosaccharides, *e.g.* it forms no osazone and does not reduce Fehling's solution. On heating with acetic anhydride it yields an octa-acetyl derivative. By the preparation of octamethyl sucrose followed by hydrolysis, which occurred without optical inversion, and identification of the fragments as 2 : 3 : 4 : 6-tetramethyl glucose and 1 : 3 : 4 : 6-tetramethyl fructose, Haworth¹ and his co-workers showed that sucrose was a D-glucopyranosido-D-fructofuranoside.



Glucose residue



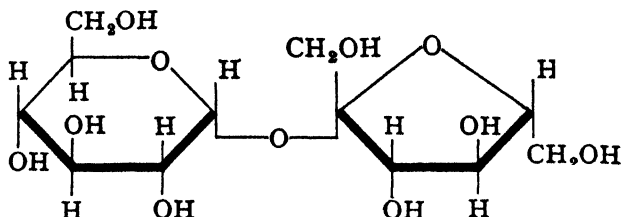
Fructose residue.

The syrupy dextrorotatory tetramethyl fructofuranose, which was identified by oxidative degradation methods, was isolated more readily from heptamethyl sucrose.

An enzymatic synthesis of sucrose from glucose-1-phosphate and fructose using an enzyme from *Pseudomonas saccharophila* has recently been reported by W. Z. Hassid and his collaborators.² It may

¹ Avery, Haworth and Hirst, *J.*, 1927, 2308; Haworth, Hirst and Nicholson, *ibid.*, 1513; Haworth, Hirst and Learner, *ibid.*, 2432. ² W. Z. Hassid, M. Doudoroff, and H. A. Barker, *J.A.C.S.*, 1944, 66, 1416.

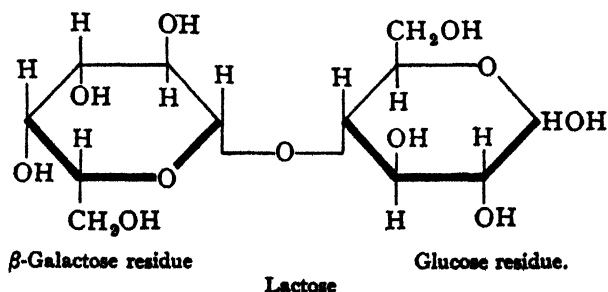
be noted that the fructose residue in this case possesses the labile 1:4- and not the normal 1:5-oxidic ring, and that the aldehydic and ketonic groups of glucose and fructose have entered into mutual glycosidic combination. From a study of optical rotations and for other reasons the α -linkage is ascribed to the glucose portion and the β -linkage to the fructose. Sucrose is therefore designated 1- α -D-glucopyranosido-2- β -D-fructofuranose.



Milk Sugar, lactose, lactobiose, is found almost exclusively in the milk of mammals. It is prepared industrially from whey, obtained as a by-product in the manufacture of cheese from milk. The whey is evaporated in vacuum pans until crystallisation sets in, and the crude milk sugar so obtained is purified by recrystallisation from water with the addition of animal charcoal.

It forms hard rhombic crystals containing one molecule of water, which become anhydrous at 140° and then melt with decomposition at 205° . It is dextrorotatory and undergoes mutarotation. On hydrolysis it decomposes into D-galactose and D-glucose. Lactose forms an osazone and reduces Fehling's solution.

The structure was proved by Haworth and his co-workers to be 4- $[\beta$ -D-galactosido]-D-glucopyranose. Crystalline heptamethyl methylactoside gave on hydrolysis 2:3:4:6-tetramethyl galactose and 2:3:6-trimethyl glucose, thus showing the galactose residue to be in the non-reducing portion of the molecule. Oxidation of lactose with bromine water gave lactobionic acid, a monobasic acid, from which complete methylation gave methyl octamethylactobionate, hydrolysis of which gave tetramethyl galactopyranose as before and 2:3:5:6-tetramethyl gluconic acid (identified as the crystalline γ -lactone). This proved the biose link to be at C₄ on the glucose residue. Since lactose is hydrolysed



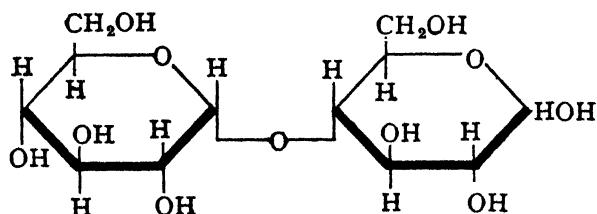
by β -glucosidase and has a low specific rotation, the β -configuration is assigned to the disaccharide linkage.

Lactose has been synthesised by C. S. Hudson and his collaborators.¹

Lactose is not as sweet as cane sugar. It is used in medicine, in the silvering of mirrors, and is frequently added to milk intended for infant consumption. It is not easily fermented with yeast but readily undergoes lactic acid fermentation, which is responsible for the souring of milk.

Malt Sugar, maltose, maltobiose, is produced by the action of diastase on starch (see p. 154) and is an intermediate product in the preparation of alcohol and alcoholic liquors. It is also an intermediate in the digestion of starchy foods, since the saliva contains an enzyme, *ptyalin*, which converts starch into maltose.

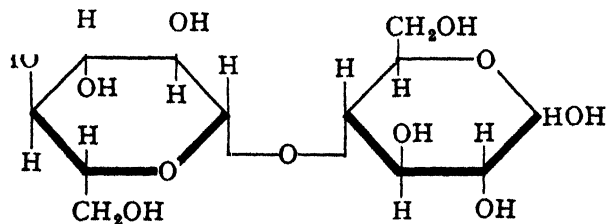
Maltose crystallises from water in small needles (1 mol. H_2O), which melt at 100° when rapidly heated. It is strongly dextrorotatory, and on hydrolysis with dilute acids yields D-glucose alone. It gives the same reactions as the monosaccharides, reducing Fehling's solution and forming an osazone. In these respects maltose resembles lactose.



Maltose

The structure of maltose was shown to be 4-[α -D-glucosido]-D-glucopyranose by Haworth and Peat.² The fully methylated disaccharide yielded 2 : 3 : 4 : 6-tetramethyl and 2 : 3 : 6-trimethyl glucose on hydrolysis. The maltobionic acid produced from maltose by oxidation gave a methyl octamethylmaltobionate, hydrolysis of which gave 2 : 3 : 4 : 6-tetramethyl glucose and 2 : 3 : 5 : 6-tetramethyl gluconic acid. The biose union is α from a consideration of the high optical rotation of maltose and the hydrolysis by maltase, specific for α -glucosides.

Cellobiose is a disaccharide obtained as the octa-acetate by the acetolysis of cellulose and is important from the point of view of assigning



Cellobiose

¹ W. T. Haskins, R. M. Hann, and C. S. Hudson, *J.A.C.S.*, 1942, 64, 1852.

and Peat, *J.*, 1946, 3094. ² Haworth

a structure to cellulose. Cellobiose was proved by methods similar to those outlined above to be 4- $[\beta$ -D-glucosido]-D-glucopyranose and thus differs from maltose in its glycosidic configuration in which it resembles lactose.

Cellobiose has also been synthesised by C. S. Hudson and his co-workers by a method which proves its structure; it had previously been synthesised by Freudenberg and Nagai.

Gentiobiose and Melibiose.—These disaccharides are obtained from the trisaccharides gentianose and raffinose respectively. Gentiobiose is 6- $[\beta$ -D-glucopyranosido]-glucopyranose and melibiose is 6- $[\alpha$ -D-galactopyranosido]-glucopyranose. Both have been synthesised by Helferich and his co-workers.

Another disaccharide, **rutinose**, 6- $[\beta$ -L-rhamnosido]-D-glucose, occurs as part of the rutin molecule.

Trisaccharides, $C_{18}H_{32}O_{16}$

Few examples of this group of polysaccharides have been discovered, the best known representative being **raffinose**, **melitose** or **melitriose**, which forms the chief constituent of Australian manna. It also occurs in beetroot, and is consequently found in beet molasses. Raffinose crystallises in fine needles with five molecules of water of crystallisation, which are driven off at 120°. On hydrolysis it takes up two molecules of water, yielding an equimolecular mixture of D-fructose, D-glucose, and D-galactose. Raffinose shows none of the reactions of the monosaccharides, and it is built up from the above three sugars in such a manner that all three carbonyl groups are modified by intramolecular linkage.

III.—POLYSACCHARIDES $(C_6H_{10}O_5)_n$ ¹

As has already been stated on p. 300, the formula of these compounds is usually expressed as $(C_6H_{10}O_5)_n$. It was shown by Kiliani that this is not a correct representation of their composition. Properly speaking, the formula is $(C_6H_{10}O_5)_n \cdot H_2O$, in which the value of n is not known with certainty. The majority of the polysaccharides are amorphous, tasteless compounds, some of which are insoluble in water. When hydrolysed by boiling with dilute acids, or by treatment with enzymes, they are all converted into monosaccharides, which may be either hexoses or pentoses. The polysaccharides are therefore considered to be built up from hexoses and pentoses by means of oxygen linkings, in the same manner as the di- and trisaccharides. The presence of hydroxyl groups is shown by their property of forming acetyl and methyl derivatives and nitric esters.

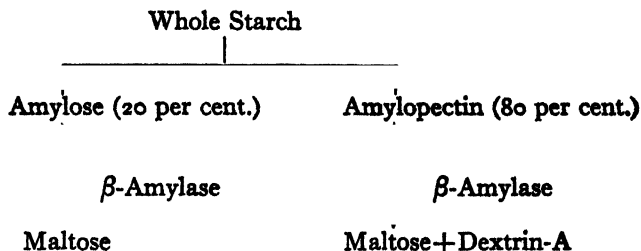
Polysaccharides are found widely distributed in the plant and animal kingdoms. But whereas in the animal organism only a few polysaccharides, *e.g.* **glycogen** and **cellulose**,² have so far been discovered, the number in the plant world is very great. In the latter source they function not only as a storehouse of carbohydrate food, but also form the chief constituents of cell membrane and supporting tissue; in the animal organism these

¹ R. L. Whistler and C. L. Smart, *Polysaccharide Chemistry* (Acad. Press, Inc. 1953).

² **Tunicin**, an "animal cellulose," occurs in the mantle or leathery skin of the tunicata, found in shallow sea-water.

parts are composed mainly of proteins. Polysaccharides of animal origin are mostly built up of glucose ; those from vegetable sources may yield in addition other monosaccharides on hydrolysis.

Starch, *amylum*, occurs very widely distributed in the vegetable kingdom. Among the raw products used industrially in the preparation of starch may be mentioned the grain or fruit of wheat, maize, rice and horse-chestnut, the tubers of the potato and the pith of the sago palm. In these the starch is stored as granules, which vary in form and size according to the nature of the plant. Under the microscope the grains may be seen to consist of an inner nucleus, around which are deposited concentric layers. The starch granules are not homogeneous but contain two very similar polysaccharides, namely **amylose** (10-20 per cent. in maize starch), which may be leached out with water at 60-80° and **amylopectin** (80-90 per cent.), which is insoluble in cold water, but forms "starch pastes" with hot water. Although amylose may be dissolved out from the starch granule, when separated from the amylopectin it "retrogrades" and becomes insoluble in water. It is completely hydrolysed by β -amylase



to give maltose, and gives a deep blue colour with iodine. Amylopectin, on the other hand, is only hydrolysed to maltose by β -amylase to the extent of 60 per cent. and a portion, Dextrin-A, which is relatively resistant to the enzyme. Amylopectin gives a reddish purple colour with iodine.

Starch is a white hygroscopic powder, with neither taste nor smell. It is insoluble in cold water, but in hot water it forms a paste which rotates the plane of polarisation to the right. This paste-forming property is due to the presence of amylopectin. In addition to carbohydrate both amylose and amylopectin contain a small amount of combined phosphoric acid, which varies in amount with the origin of the starch but in general does not exceed 0.2 per cent. (calculated as P_2O_5).

A peculiarity of starch is the blue colour it yields with iodine in the presence of a little potassium iodide or hydriodic acid. This is a very sensitive test. When boiled with dilute acid, starch is first transformed into a soluble gummy mixture of products known as *dextrin*, and finally into D-glucose. Under suitable conditions the conversion is quantitative. **Dextrin** is manufactured by heating starch alone, or in the presence of a little nitric acid, to 110°, and is used as a mucilage under the name of "British gum." Concentrated nitric acid dissolves starch with the formation of nitric esters.

As has already been emphasised, starch is one of the most valuable constituents of food, and also forms the basis of the brewing industry and the manufacture of dextrin. It is employed in laundry work as a stiffening and for giving a finish to textiles, as an adhesive (starch paste), as a thickening agent for colours in calico printing, and for sizing paper.

Glycogen, animal starch or liver starch occurs in the animal organism,¹ where, like starch in the vegetable kingdom, it functions as a carbohydrate reserve. It can be isolated from liver as a white amorphous powder, but is also present in muscular tissue and in other parts of the organism. During muscular effort the glycogen content of the muscle diminishes, owing to its conversion into lactic acid.² On hydrolysis with acids or ferments glycogen finally yields D-glucose. Glycogen differs from starch in dissolving to an opalescent solution in cold water, and in giving with iodine a reddish-brown coloration. It is very stable towards hot alkalis, and is precipitated with alcohol. All preparations of glycogen appear to exhibit weak reducing powers towards Fehling's solution.

Inulin is a polysaccharide found in the roots of the dahlia, chicory and various *Compositae*. It is coloured yellow by iodine, and on hydrolysis is converted quantitatively into D-fructose.

Pectins are very complex gelatinising compounds which are found widely distributed in nature, especially in fruit juices. Pectins yield on degradation a mixture of polysaccharides including *pectic acid*, a poly galacturonic acid, which has a chain-like structure as in cellulose

The Molecular Structure of Polysaccharides.³

Starch, Glycogen, Inulin and Cellulose

The polysaccharides were first regarded as micelles. A new concept, however, was introduced by H. Staudinger who, from his studies on the formaldehyde polymers with their long chains of repeating units, suggested that cellulose might also be a long-chain molecule. This was substantiated by X-ray investigation which showed cellulose to be essentially crystalline with glucose units arranged in long chains (Sponsler and Dore). Finally, Haworth in 1927 advanced the correct formula which has since been universally accepted. Subsequent research has shown that not only cellulose but all polysaccharides are large molecules in which the constituent atoms are held together by the same forces as obtain in small molecules.

The structural investigations of the polysaccharides have been beset by difficulties somewhat similar to those encountered in the protein field. Purification is not easy and for this reason cellulose and starch, which

¹ An unusual case of the occurrence of glycogen in a plant source (the seed of sweet corn, *Zea Mays*) was recorded by D. L. Morris and C. T. Morris, *J. Biol. Chem.*, 1939, 130, 535, and W. Z. Hassid and R. M. McCready, *J.A.C.S.*, 1941, 63, 1632. ² Bell, *Carbohydrate Biochemistry* (Univ. Tutorial Press, 1952), Chapters V and VI. ³ Haworth, *Chemistry and Industry*, 1935, 54, 859.

can be obtained in the pure condition, have been most investigated. Even with pure starting material, however, formidable tasks confront the investigator for the obviously complex structures can be ascertained only by determining the fundamental structural units in the polysaccharides; their mode of binding and the order in which they occur in the molecule; and the molecular weight.

In the sequel we shall consider mainly the elucidation of the structure of starch and cellulose.

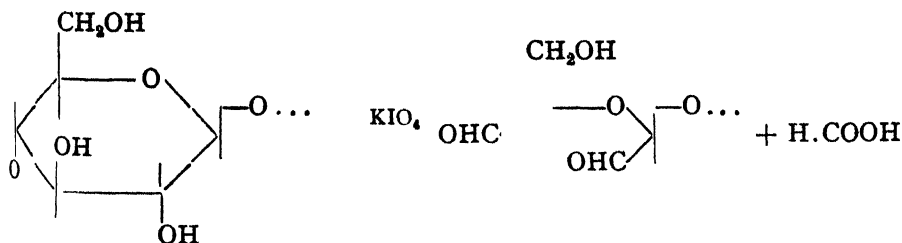
Of the methods used in structural determinations of the polysaccharides four may be briefly mentioned.

(1) Hydrolytic breakdown of the molecule is effected by acids. Fission occurs at the glycosidic linkages, starch, for example, yielding glucose. When mixtures of products are obtained, advantage is taken of the method of partition chromatography. In this way complex mixtures of sugars and their methylated derivatives may be separated quantitatively even on the milligram scale.

(2) Partial hydrolysis can be effected by enzymes. We have already had an example of this in the enzymatic breakdown of starch to maltose (p. 327).

(3) Methylation methods. Polysaccharides can be methylated and the product then hydrolysed to partially methylated sugars. Only those hydroxyl groups will be methylated which are not engaged in glycosidic linkages. Consequently the unmethylated hydroxyl groups in the hydrolytic products denote the points of attachment of the sugar units in the polysaccharide.

(4) Periodic acid oxidation. A valuable application of this oxidising agent is in the detection and estimation of terminal sugar residues in polysaccharides.¹ This is exemplified by the oxidation of cellulose by potassium periodate. Each of the end groups is oxidised to formic acid.

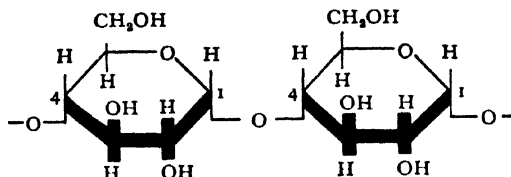


and from the quantity of formic acid thus formed it is possible to calculate the molecular weight of cellulose.

Starch.—As in the case of the relatively simple di- and trisaccharides, valuable information concerning the structure of the complex polysaccharides has been obtained by examining the behaviour of the parent compounds and their methyl derivatives towards hydrolytic agents.

¹ F. Brown, S. Dunstan, T. G. Halsall, E. L. Hirst, and J. K. N. Jones, *Nature*, 1945, 156,

Thus starch may be converted quantitatively into D-glucose by heating it with dilute mineral acid. Similarly, on treatment with diastase or amylase it forms maltose in 80 per cent. yield. In view of the known structure of maltose as a glucose- α -glucoside (p. 327), the possibility suggested itself that the starch molecule is built up of a series of α -glucose units joined through carbon atoms 1 and 4 by glycosidic links (compare



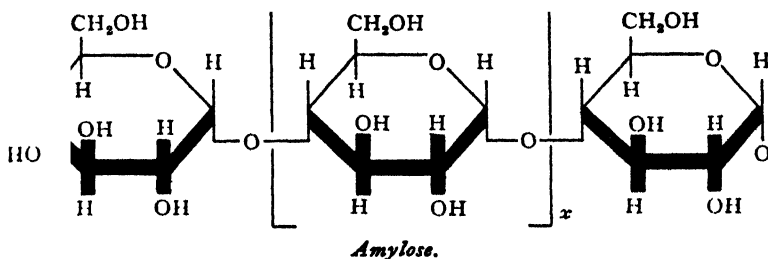
formula VII for α -glucose on p. 316). Definite support for this assumption was obtained later from investigations on methylation products of starch. Completely methylated starch (trimethyl starch) was found to give on hydrolysis an almost theoretical yield of 2:3:6-trimethyl glucose. This is seen to be in entire agreement with the above formula, in which only the hydroxyl groups in positions 2, 3 and 6 are open to attack by the methylating agent. By the acetolysis at 15° of methylated starch (and glycogen) with acetyl bromide, followed by oxidation and further methylation, Haworth and Percival obtained in 22 per cent. yield a methyl octamethyl maltobionate, the structure of which was proved as described under maltose. This proved the maltose unit to be a constituent part of the starch chain, the mild conditions precluding the possibility of a reversion-synthesis from glucose, a possibility which can never be entirely excluded from hydrolysis involving enzymic or acid hydrolysis.

Further information on the constitution of starch has been provided by research on its components, amylose and amylopectin.

Amylose. Amylose can be obtained in the crystalline state. It is hydrolysed to maltose (70 per cent. conversion) by crystalline sweet potato β -amylase, but if an enzyme (Z-enzyme) is also present 100 per cent. conversion occurs.¹ It has a molecular weight lying between 10,000 and 50,000. When it is methylated and the product hydrolysed 2:3:6-trimethyl glucose is obtained. Admixed with a large amount of this is a small quantity of 2:3:4:6-tetramethyl glucose, each of the two hydrolytic fragments being present in the form of its methyl glucoside as the result of further interaction with the hydrolysing medium. Now if the constituent monosaccharide units were originally joined together in a closed loop, only one type of methylated sugar should be formed when the loop is disrupted by hydrolysis. The presence of tetramethyl glucopyranose, on the other hand, indicates that an open chain is present and that one of the terminal α -glucose residues is thus capable of becoming more highly methylated than the remaining units. This is illustrated by

¹ S. Peat, S. J. Pirt and W. J. Whelan, *J.*, 1952, 705.

the following formula for amylose, in which the terminal group on the left yields a molecule of tetramethyl glucose, and the central portion x molecules of trimethyl glucose. The right-hand end group gives rise to the methyl glucoside of trimethyl glucose, but this indicates no differentiation from the central part of the molecule since, as has already been stated, under the conditions of experiment all the glucose residues are



eventually isolated in the form of their methyl glucosides. Osmotic pressure measurements indicate a molecular weight of about 50,000 for amylose and this is in agreement with the value derived from the observation that methylated amylose on hydrolysis yields about 0.3 per cent. of tetramethyl glucose corresponding to about 300 glucose units in the molecule.¹

Recent work by Peat *et al.* (*loc. cit.*) indicates that some branching occurs in amylose.

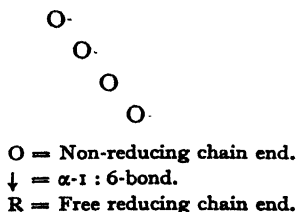
Amylopectin. Amylopectin is the main component of starch and is responsible for the formation of starch pastes. Its separation in the pure state is lengthy and difficult.

The molecular weight of amylopectin is much greater than that of amylose and has been found by osmotic pressure measurements to be about 500,000, corresponding to a molecule built up of 3000 glucose units. Now from the quantity of 2 : 3 : 4 : 6-tetramethyl glucose (4.5 per cent.) formed along with the main product 2 : 3 : 6-trimethyl glucose (90 per cent.)² and from the amount of formic acid obtained by oxidation with potassium periodate³ it is found that there is one non-reducing end-group for every 20-25 glucose units in the molecule. If the lower figure is taken this means that there are 150 end groups in each molecule and the amylopectin molecule must therefore be highly branched. This agrees with the failure of amylopectin to crystallise or form threads.

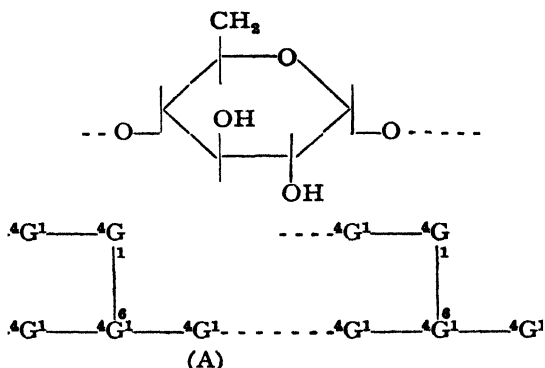
Later research has shown that amylopectin can be represented by a laminated structure of the type shown in the diagram. Each repeating unit of *ca.* 20 glucose residues is indicated by a straight line ending in an arrow head corresponding to the reducing group. Absence of reducing properties is accounted for by the reducing group being joined by a

¹ W. Z. Hassid and R. M. McCready, *J.A.C.S.*, 1943, 65, 1157. ² R. M. McCready and W. Z. Hassid, *J.A.C.S.*, 1943, 65, 1157. ³ F. Brown, T. G. Halsall, E. L. Hirst and J. K. N. Jones, *J.*, 1948, 27.

glycosidic linkage to a primary alcohol group (C_6) of a glucose unit in an adjacent chain (see formula). Evidence in support of this point



is obtained by a further examination of the hydrolysis products from methylated starch. In addition to the main component, 2 : 3 : 6-trimethyl glucose, 2 : 3-dimethyl glucose was isolated in about the same amount as tetramethyl glucose from the end-group. Since carbon atom C_4 is employed in linking together the units in the main chains, C_6 must be



the position at which these chains are aggregated. The main features of the amylopectin structure are shown in the diagram (A) in which G represents the glucose unit and the numbers show the linkages involved.

When the molecular model corresponding to the formula of starch is examined, it is seen that owing to the valency angles of the α -glucosidic links the spatial distribution of the monosaccharide units is not linear, but a twisted structure which would be expected to facilitate the aggregation and interlocking of the molecules. This fact may explain the characteristic physical differences shown by starch and cellulose, the latter being represented by long straight macro-molecules of a thread-like nature.

Synthetic Starch and Amylose.—During the past few years it has been discovered that *glucose-1-phosphate* (α -glucopyranose-1-phosphoric acid) can undergo reversible transformation into a polysaccharide in the presence of *phosphorylases*, which are enzymes occurring in various animal and vegetable sources such as muscle, liver, yeast and potatoes.

Cori, Kiessling and others, working principally with enzymes from animal tissues and from yeast, have concluded that glycogen¹ is formed *in vivo* from the glucose ester.

Glucose-1-phosphate

glycogen+free phosphate.

Hanes,² using a purified phosphorylase from potato juice, has succeeded in converting glucose-1-phosphate in high yield into a starch, which strongly resembles natural starch and is still more closely identified with the amylose obtainable from the natural product. The synthetic starch deposits in granular form and has a high rotation, $[\alpha]_D$ being about 200°. It gives a more intense blue with iodine than whole starch and is less soluble in water. From aqueous solutions it tends to deposit again, except when present in high dilution. Like certain other polysaccharides it dissolves in strong alkalis. With α -malt-amylase the synthetic starch undergoes hydrolysis in the same manner as natural starch, but with β -amylase (from germinating barley) it is completely hydrolysed, whereas the hydrolysis of amylopectin ceases after 60 per cent. conversion. In these points of difference the synthetic product closely resembles the less soluble "amylo-amylose" fraction of whole natural starch, which behaves in the same way towards β -amylase and also tends to deposit from aqueous solution. Astbury, Bell and Hanes have carried out an X-ray examination and find that the patterns of the natural and synthetic starches are essentially the same. Further investigations by end-group analysis by Haworth and his co-workers and by W. Z. Hassid and R. L. McCready have shown that the synthetic starch undoubtedly consists of very long chains of glucose units since the proportion of tetramethyl glucopyranose was much smaller than required for the repeating unit of 20 units in amylopectin. The synthetic starch appears to be closely related to the amylose fraction of starch, the chain length of which is 300 glucose units. Hassid has also determined the chain length of amylose from potato starch to be of approximately 350 glucose units, whereas amylopectin from the same source possesses a repeating unit of 25 glucose units, in agreement with the earlier determinations of the Birmingham school.

A polysaccharide, also apparently identical with amylose, has been obtained by the action of crystalline muscle phosphorylase on glucose-1-phosphate *in vitro* by Hassid, G. T. Cori, and R. M. McCready,³ which is made up of unbranched chains of about 200 glucose units. W. N. Haworth and his co-workers⁴ have reported the enzymatic synthesis of a product resembling amylopectin from glucose-1-phosphate.

¹ C. F. Cori and G. T. Cori, *Proc. Soc. Exptl. Biol. Med.*, 1936, 34, 702. C. F. Cori, *J. Biol. Chem.*, 1940, 26, 285. W. Kiessling, *Biochem. Z.*, 1939, 202, 50. ² C. S. Hanes, *Proc. Roy. Soc., Lond.*, 1940, B128, 421; B129, 174. Hanes suggests that the polysaccharide examined by the above workers may have been more closely related to a starch than to glycogen. ³ W. Z. Hassid, G. T. Cori and R. M. McCready, *J. Biol. Chem.*, 1943, 248, 89. ⁴ W. N. Haworth, S. Peat and E. J. Bourne, *Nature*, 1944, 154, 236. E. J. Bourne and S. Peat, *J.*, 1945, 877.

Mechanism of Alcoholic Fermentation¹

Researches over a period of years have shown that alcoholic fermentation is a complex process in which a number of distinct reactions occur, each of which is promoted by a specific enzyme in the living cell. Many of the intermediates are phosphates and indeed phosphate transference plays an important role in fermentation. Another important reaction is the transference of two hydrogen atoms from one molecule to another. In these changes two co-enzymes take a prominent part. *Adenosine triphosphate* (ATP) is both a phosphate carrier and a phosphate supplier,

Emden-Meyerhof Mechanism of Alcoholic Fermentation

Reactions.	Reaction Type.	Enzyme and Coenzyme.
Glucose		
↓ ↑	Phosphate transfer	Hexokinase
Glucose-6-phosphate		ATP ↓
↓ ↑	Isomerisation	ADP
Fructose-6-phosphate		
↓ ↑	Phosphate transfer	Phosphohexokinase
Fructose-1 : 6-diphosphate		ATP ↓
↓ ↑	Breakdown	ADP
Glyceraldehyde-3-phosphate		
↓ ↑	Phosphate transfer and oxidation	DPN ↓
1 : 3-Diphosphoglyceric acid		DPN—H
↓ ↑	Phosphate transfer	ADP ↓
3-Phosphoglyceric acid		ATP
↓ ↑	Isomerisation	
2-Phosphoglyceric acid		
↓ ↑	Dehydration	Enolase
2-Phosphoenolpyruvic acid		
↓ ↑	Phosphate transfer	ADP ↓
Pyruvic acid		ATP
↓ ↑	Irreversible decarboxylation	
Acetaldehyde + CO ₂		
↓	Hydrogenation	DPN—H ↓
Ethyl alcohol		DPN

ADP = Adenosine diphosphate

ATP = Adenosine triphosphate

DPN = Diphosphopyridine nucleotide

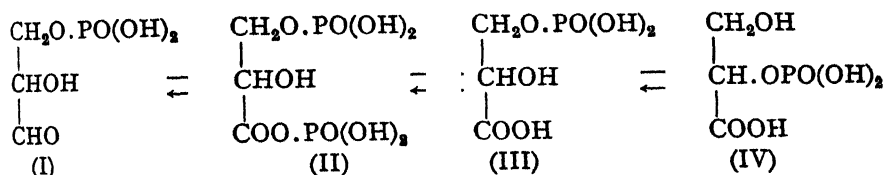
DPN—H = Dihydro-derivative of DPN

¹ See F. F. Nord, *Chem. Rev.*, 1940, 26, 423. W. Kermack, *Science Progress*, 1949, 283. E. Baldwin, *Dynamic Aspects of Biochemistry*.

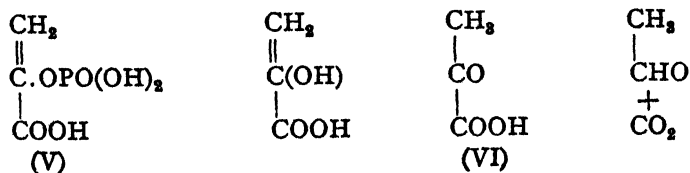
being converted in the process into *adenosine diphosphate* (ADP). The other co-enzyme is *diphosphopyridine nucleotide* (DPN) which serves as a hydrogen carrier in the form of its dihydro-compound, DPN-H.

Broadly speaking, the fermentation process goes through the following stages: starch \rightarrow glucose \rightarrow hexose phosphates \rightarrow triose phosphates and related compounds \rightarrow pyruvic acid \rightarrow acetaldehyde \rightarrow ethyl alcohol. The first stage in the breakdown of glucose is the formation of glucose-6-phosphate. This is converted by a two-stage process to fructose-1 : 6-diphosphate, often called the Harden-Young ester after the investigators who isolated it from the fermentation products obtained by the action of cell-free yeast juice, "zymase," on a mixture of glucose and inorganic phosphate.

Fructose-1 : 6-diphosphate undergoes a reverse aldol condensation to yield the triose phosphates glyceraldehyde-3-phosphate (I) and dihydroxyacetone-phosphate, the former of which is dehydrogenated and phosphorylated in the presence of inorganic phosphate and the co-enzyme DPN. The products are 1 : 3-diphosphoglyceric acid (II) and DPN-H. The diphosphoglyceric acid is then dephosphorylated to 3-phosphoglyceric acid (III) ADP being simultaneously phosphorylated to ATP. Isomerisation of the 3-acid gives 2-phosphoglyceric acid (IV) which by loss of



water affords 2-phosphoenolpyruvic acid (V), *i.e.* the phosphate of the enolic form of pyruvic acid. Hydrolysis gives pyruvic acid (VI).



In the last stages pyruvic acid breaks down in the presence of carboxylase into acetaldehyde and carbon dioxide, and the aldehyde is stabilised by reduction to ethyl alcohol. This final stage is a complicated process which may be regarded as the concurrent hydrogenation of the aldehyde and dehydrogenation of DPN-H to DPN in the presence of alcohol dehydrogenase.

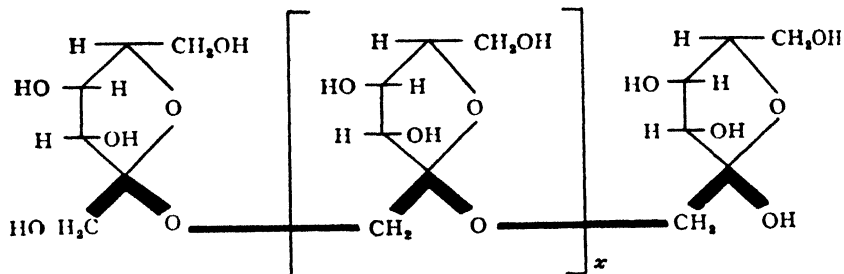
Glycogen.—The constitution of glycogen (p. 330) was determined in a similar manner¹ to that of starch. This compound resembles starch in many of its chemical properties, being converted quantitatively into

¹ Haworth and E. G. V. Percival, *J.*, 1932, 2277. Haworth, Hirst and Smith, *J.*, 1939, 1914.

glucose on acid hydrolysis and forming maltose with diastatic ferments. The molecule thus consists of α -glucose units linked together in the same manner as in maltose. In this case, however, the repeating unit is smaller and the proportion of tetramethyl glucose obtained from methylated glycogen indicates that the chains only contain in most cases 12 and in some cases 18 glucopyranose units depending on the source, and corresponding to a yield of *ca* 9 per cent. and 7 per cent. of tetramethyl glucose from the methylated polysaccharide.

The molecular weight determined by osmotic pressure measurements is very high—in the region of 1 to 2 millions. The structure of glycogen may be represented in the same way as that of amylopectin, the size of the repeating units being, of course, different.

Inulin (p. 330) differs from the above compounds in possessing a fundamental unit of fructofuranose. When methylated and submitted to hydrolysis, inulin yields a mixture of 3 : 4 : 6-trimethyl fructofuranose together with about 3.7 per cent. of 1 : 3 : 4 : 6-tetramethyl fructofuranose.¹ It is therefore concluded that the inulin molecule has the structure



Inulin.

The tetramethyl fructofuranose is derived from the monosaccharide unit at the left-hand end of the formula, and from the proportion present in the hydrolysis mixture it is estimated that the molecule contains about 30 fructofuranose residues, and thus has a molecular weight of approximately 5000. This value is in agreement with that previously obtained for unmethylated inulin by physical methods, hence there is no aggregation of the "chemical units" such as occurs with starch.

Cellulose² forms the chief constituent of the cell walls of all plants. It is therefore obtainable in quantity from many natural products, among which the following rank highest in industrial importance: wood, the chief constituent of which is cellulose; cotton wool, distinguished by its fineness and purity; also flax, hemp, nettles and other substances. Cellulose possesses an organised tubular structure, which shows distinct minor differences according to the source of the material.

¹ Haworth, Hirst and E. G. V. Percival, *J.*, 1932, 2384. ² See *Researches on Cellulose*, 1910-1921, Cross and Dörée (Longmans); *The Biochemistry of Cellulose, the Polyuronides, Lignin, etc.*, by A. G. Norman (Oxford, 1937); E. Ott in *Chemistry of Large Molecules*, Chapter V (Interscience Publishers Inc., New York, 1943).

In order to obtain pure cellulose, the cellular tissue of plants, preferably cotton wool, is treated in succession with dilute alkali, dilute acid, water, alcohol and ether. Under these conditions impurities and incrustations are removed, and the cellulose, which is very stable towards dilute acids and alkalis, is obtained as a white amorphous mass. Textiles such as cotton and linen consist almost entirely of cellulose, and the finest Swedish filter paper is an almost chemically pure form.

Cellulose is insoluble in the usual solvents, but dissolves in *Schweizer's reagent* made by dissolving copper hydroxide in ammonia. From this solution cellulose may be precipitated as a jelly by addition of acids, salts, etc., and on washing with alcohol is then obtained as a white amorphous powder. A similar solvent power is possessed by a solution of copper carbonate in ammonia, zinc chloride dissolved in hydrochloric acid, and diethyl-dibenzyl-ammonium hydroxide.

By suitable treatment with acids, cellulose may be transformed into *hydrocellulose*. This is frequently used in place of cellulose in technical processes requiring cellulose as raw material.

With strong sulphuric acid cellulose swells up and passes gradually into solution, from which the addition of water precipitates a substance *amyloid*, resembling starch. On prolonged treatment with strong sulphuric acid, followed by boiling with dilute acid, cellulose undergoes complete hydrolysis, yielding first cellodextrins, and eventually D-glucose. Under certain conditions the hydroxyl groups of cellulose interact with acids with the production of *esters*, of which the nitrates and acetates are of outstanding importance. Cellulose ethers such as ethyl cellulose and benzyl cellulose are also of considerable technical value.

Constitution of Cellulose.—Analysis shows that cellulose is an anhydroglucose ($C_6H_{10}O_5$)_n. Knowledge of the constitution of cellulose has been obtained by the use of hydrolytic methods. Such degradations are the result of two simultaneous processes: depolymerisation of the fundamental units of the cellulose molecule, and disruption of these units to reducing sugars. Hydrolysis of cellulose gives only glucose, Monier-Williams, for example, by means of sulphuric acid, isolating crystalline glucose in a yield greater than 90 per cent. This was confirmed by Irvine and Soutar, who, by acetylation with acetic anhydride and sulphuric acid followed by heating with methanolic HCl, obtained a 92 per cent. yield of the crystalline methyl glycosides.

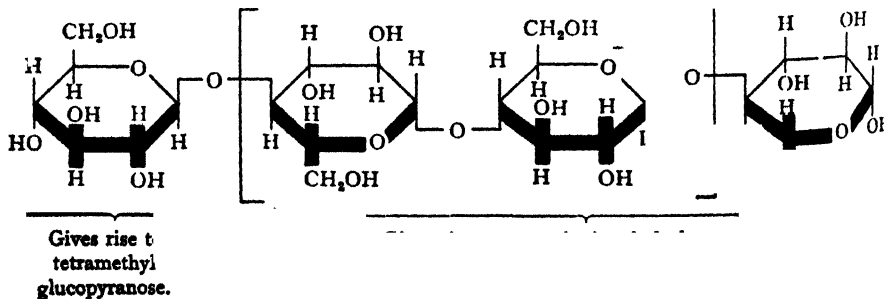
Cellulose contains three hydroxyl groups for each glucose unit, since it forms on acetylation a triacetate, and on methylation with dimethyl sulphate and alkali gives 2 : 3 : 6-trimethyl glucose (90 per cent. yield). Furthermore, cellulose when treated with a mixture of acetic anhydride and acetic acid undergoes *acetolysis* (hydrolysis and acetylation) to give octa-acetyl cellobiose (p. 327). All these observations can be accommodated if the cellulose molecule is composed of β -glucopyranose residues united by 1 : 4-linkages as in cellobiose.

Additional evidence for this view came from a number of investigations.

Under suitable conditions cellulose may be hydrolysed to cellobiose in 60 per cent. yield, which, if allowance is made for side-reactions, corresponds to an almost complete conversion of cellulose into cellobiose. In another investigation W. N. Haworth, E. L. Hirst and H. A. Thomas obtained additional support for this view by the acetolysis of methylated cellulose at 15° C. to give, after further methylation, three crystalline products—heptamethyl- β -methylcellobioside (18 per cent.), a decamethyl- β -methylcellotrioside (15 per cent.), and a methylated cellodextrin. Hydrolysis of the methylated cellotrioside gave two molecules of 2:3:6-trimethyl glucose and one of tetramethylglucopyranose. Further acetolysis of the methylated cellodextrin and methylation gave heptamethyl β -methylcellobioside. These results indicate a progressive breakdown of the cellulose chain and prove that at least three consecutive β -glucopyranose units are present in cellulose. Haworth and Machemer then investigated the composition of cellulose by the end-group method (see starch p. 332). This was the first of such assays to be carried out. Careful hydrolysis of methylated cellulose with cold saturated hydrochloric acid gave a mixture of methylated glucoses, which was analysed by conversion into the corresponding methyl glucosides followed by fractional distillation in a high vacuum. In this manner the main product, *trimethyl glucose*, was found to be mixed with a small amount of *tetramethyl glucose*. From the presence of the latter it was inferred that, as in the case of starch, the molecules are terminated chains and not endless loops. Furthermore, the proportion of tetramethyl glucose in the mixture leads to a value of between 100 and 200 β -glucose units for the length of the chain, indicating a molecular weight of the order 20,000-40,000 for the particular cellulose preparation employed. This is regarded as an average lower limiting value.

A more reliable chemical method for determining the number of glucose units in the molecule is provided by periodate oxidation (p. 331), which showed that the cellulose molecule contains about 1000 glucose units.

A model of the formula thus deduced for cellulose shows the molecules



to be represented by long straight lines, in agreement with the characteristic appearance of the natural cellulose fibre (contrast starch, p. 314). This structure is also confirmed by various X-ray examinations.

cellulose, the β -glucopyranose unit being the only possibility with the correct dimensions to fit the unit cell which is $8.35 \times 10.3 \times 7.9$ Å. A cellobiose unit is to be found along with each of the edges (10.3 Å) of the structure and one is in the centre of the cell. The plane of the pyranose rings is almost parallel to the faces of the cell in native cellulose, but after the process of mercerisation the chains rotate slightly and the dimensions become $8.1 \times 10.3 \times 9.1$ Å. With this fact is no doubt connected the lustre and dye absorbing capacity of mercerised cellulose.¹ It has been estimated² from the breadth of the lines measured along the fibre axis in the X-ray diagram of native ramie cellulose that the minimum molecular weight is 20,000. This value is of the same order as that determined chemically by end-group analysis.

Later experiments³ on the methylation of cellulose with methyl sulphate and sodium hydroxide have revealed some interesting new facts. After five methylations conducted in an atmosphere of nitrogen no tetramethyl glucose end-group could be detected and the molecular weight deduced from measurements of the specific viscosity and osmotic pressure corresponded to 1300 glucose units, as compared with 150-170 units after six methylations in air as determined both by the end-group assay and by physical methods. Further methylations in a nitrogen atmosphere led to disaggregation, however, since the determination of molecular weight by the physical methods gave a value of about 200 glucose units after 25-30 methylations; the product still contained no end-groups detectable as tetramethylglucopyranose. According to experimental conditions, therefore, methylated celluloses may be formed which are either terminated chains of glucose or closed chains with no terminal glucose unit.

Pending further information it is suggested that the cellulose structure is represented by long parallel chains of the type illustrated above, so orientated that alternate chains are arranged with their potential reducing groups pointing in opposite directions; the ends of the chains are supposed to be united in pairs to form long closed loops, whose semi-rigid parallel alignment is maintained by a series of bonds linking opposite sides of the loops. On methylation in nitrogen the loop may be ruptured, but this must be followed by the open ends uniting to give smaller closed loops. In air the ruptured ends apparently remain open.⁴ The assumption of the presence of cross-linkages is necessary since the joining of the "head" to "tail" in a disaggregated unit could not take place if the chains were distributed at random.

¹ For the X-ray investigation of cellulose see *Colloid Symposium Monograph*, New York, 1926, 174; Sponsler, *J. Gen. Physiol.*, 1926, 9, 677; K. H. Meyer and Mark, *Ber.*, 1928, 61, 593; K. H. Meyer, *Z. ang. Ch.*, 1928, 41, 935; Staudinger, *ibid.*, 1929, 42, 37, 67. ² R. O. Herzog and Krüger, *J. Phys. Chem.*, 1926, 30, 466. Hengstenberg, *Z. Krist.*, 1928, 69, 271. ³ W. N. Haworth, E. L. Hirst, L. N. Owen, S. Peat and F. J. Averill, *J.*, 1939, 1885. W. N. Haworth, R. E. Montonna and S. Peat, *ibid.*, p. 1899. ⁴ For a more detailed account see Haworth, *Chem. and Ind.*, 1939, 58, 917; S. Peat, *Ann. Rep.*, 1939, 273.

Some values for the molecular weight of various celluloses determined by the sedimentation rate in the ultracentrifuge are given below to illustrate the great size of the cellulose macromolecule as well as the effect of chemical treatment.

Molecular Weight of Various Cellulose Preparations

Preparation.	Molecular Weight.	Degree of Polymerisation. (No. of Glucose Units)
Native Cellulose . . .	570,000 ¹	3,500
Purified Cotton Linters . .	150,000-500,000 ¹	1,000-3,000
Wood Pulps	90,000-150,000 ¹	600-1,000
Unbleached Cotton . . .	1,500,000 ²	9,200
Raw Georgia	1,000,000 ²	6,200
Nettle Fibre	1,760,000 ²	10,800
Ramie Fibre	1,840,000 ²	11,300
Sulphite Pulp	400,000 ²	2,900

Acetobacter xylinum reacts with glucose to give "synthetic" cellulose, which resembles cellulose in its chemical properties.³ This product undergoes hydrolysis with acids at a rate comparable with native cellulose, forms a triacetate and a trimethyl ether, yields cellobiose octa-acetate on acetolysis, and gives an X-ray pattern similar to that of native cellulose.

Lichenin.—A polysaccharide found in Iceland Moss resembles cellulose in that it consists of a chain of unbranched β -D-glucopyranose units $(C_6H_{10}O_5)_n$ where $n = 80-160$. This substance, unlike cellulose, is water-soluble. It differs from cellulose in containing both 1 : 3- and 1 : 4-linkages.

Other Properties of Cellulose.—Towards dilute alkalis, which readily dissolve and decompose animal tissue, cellulose is extremely stable. A strong solution of caustic alkali, on the other hand, produces a curious thickening and gelatinisation of the walls of the fibre, causing the cellulose to shrink and become translucent. This reaction is used for producing crinkled surfaces on cotton fabrics, the process being known as *mercerising*, after its discoverer.⁴ Alkali celluloses, produced in the above manner by the action of concentrated alkalis, combine with carbon bisulphide to form a mixture of *cellulose xanthates* known as *viscose*.⁵ These are sodium salts of the general formula $RO.CS.SNa$, which swell up with water to a marked degree, giving a colloidal solution which has become of great importance in the manufacture of artificial silk.

¹ Kraemer, *Ind. Eng. Chem.*, 1938, 30, 1200.

² N. Gralen and T. Svedberg, *Nature*,

1943, 625. ³ J. Barsha and H. Hibbert, *Canadian J. Research*, 1931, 5, 580.

⁴ In 1844 John Mercer observed that cellulose which had been treated at the ordinary temperature with caustic soda showed, after washing and drying, an increased tenacity and power of taking up certain dyes. Later it was found that cotton so treated acquired a higher lustre, and hence mercerisation became an industrial process. This is one of the biggest discoveries in the textile industry of the nineteenth century. ⁵ Cross, Bevan and Beadle, *Ber.*, 1893, 26, 1090; 1901,

34, 4513.

As already indicated, cellulose is used industrially in a variety of ways, *e.g.* in the preparation of paper, parchment paper, collodion, gun-cotton, smokeless powder, celluloid and artificial silk.

Cellulose Nitrates, or Nitrocelluloses

A mixture of nitric and sulphuric acids interacts with cotton-wool to form nitric esters of cellulose, incorrectly but very generally known as nitrocelluloses. These still retain the structure of cotton-wool, although somewhat coarser and harder to the touch. By modifying the concentration of acid used and the length of treatment it is possible within limits to vary the number of nitric acid groups entering into the cellulose molecule. The ester with the lowest proportion of nitrogen has the composition of a mononitrate ($C_6H_7O_4(ONO_2)_n$) of cellulose, while that containing the highest proportion approximates closely to a trinitrate ($C_6H_7O_2(ONO_2)_3$). The product obtained, however, is always a mixture, and a gradual alteration in the conditions of nitration never leads to any sudden change in the proportion of nitrogen. No sharp distinction can therefore be drawn between mono-, di-, and trinitrocelluloses, and so on. An important factor is the water content of the nitrating acids; if this is increased the nitrogen content of the product decreases regularly, although not proportionally, within the above limits. Probably the nitration of cellulose leads to the formation of a mixture of compounds in which a progressively increasing number of complexes have entered into reaction. In addition to esterifying the cellulose, nitric acid also brings about hydration, leading to the formation of hydrocellulose nitrates.

Lower nitrocelluloses containing one or two nitro groups burn very much more freely than cellulose itself, but are in no sense explosive. They are grouped together under the name of **pyroxylin**, and dissolve readily in a mixture of alcohol and ether, such a solution being sold as **collodion**. The latter is extensively used in medicine, photography and the manufacture of artificial silk (see below).

If lower nitrates of cellulose are mixed with camphor and submitted to the action of heat, **celluloid** is obtained. The warm product is easily moulded, and sets to a hard, transparent mass on cooling. It is employed in the manufacture of a variety of useful and ornamental articles, but is very inflammable.¹

Celluloid may be considered as an intimate physical mixture of nitrocelluloses and camphor, and constitutes the earliest successful plastic, camphor acting as a plasticiser (see index).

The highest nitration product of cellulose has a nitrogen content of 13.4 per cent. approaching that of a cellulose trinitrate (14.14 per cent.), and is employed under the name of gun-cotton in propellant explosives and for blasting. Gun-cotton burns with extreme rapidity but only explodes when detonated, *e.g.* when combustion is initiated by means of a little mercury fulminate. For explosive purposes it may be used directly in the compressed state, as in torpedoes and in cartridges for blasting, or it may be

¹ *Cellon*, prepared from cellulose acetate (cellite) by the addition of camphor, is also less inflammable than celluloid and is used for cinematograph films.

employed mixed with nitroglycerine (p. 266). A development of great importance was the utilisation of gun-cotton and pyroxylin in the preparation of **smokeless powder**. This is based on the fact that when nitrocelluloses are treated with solvents such as acetone or ethyl acetate, even in quantity insufficient for solution, they completely lose their organised structure. Under this treatment they swell up, forming a gelatinous product, which, after removal of the solvent, gives an amorphous mass of the same chemical composition as the starting material, but possessing a much closer texture. In such a product the explosion wave is propagated with much lower velocity, thus rendering it suitable for use as a propellant. Nitrocellulose powders of this type have been adopted by the ordnance departments of almost every army. The explosive is employed in the form of small squares for rifles, and in ribbons or bundles of rods for artillery. The propellant in most general use in the British Army is cordite, which contains "nitroglycerine" in conjunction with "nitrocellulose," the ingredients together with petroleum jelly being mixed to an appropriate consistency with acetone, and the product formed forced through dies to form rods or cords after which the solvent is removed and recovered.

Artificial Silk

The preparation of artificial silk consists essentially in forcing a syrupy solution of cellulose, cellulose derivatives, or other products under high pressure through very fine apertures into a suitable medium, whereby the solvent is removed and fine threads are obtained. The threads are allowed to form under slight tension, and as soon as they have solidified are twisted or collected directly on reels, to be woven subsequently into fabrics in the same way as natural silk.

The practical difficulties of this process were first overcome in 1885 by de Chardonnet, who employed collodion as the starting material. This gave a thread consisting of nitrocellulose and therefore exceedingly inflammable. By treatment with denitrating agents, *e.g.* sodium hydrosulphide, it was found possible to replace the nitrate grouping in the nitrocellulose threads by hydroxyl without altering the form of the material. Threads consisting of cellulose or a hydrate of cellulose are thus formed, which are no more inflammable than ordinary cotton.

Cellulose threads possessing the desired silky gloss are also obtained by other methods, *e.g.* by utilising a solution of cellulose in ammoniacal copper oxide as the "spinning liquid" (Pauly's method). In this case the liquid is forced into dilute sulphuric acid, which coagulates the threads and at the same time removes copper and ammonia, yielding without any further treatment a cellulose thread.

A product known as **viscose silk** is manufactured by use of a solution of cellulose xanthates (p. 342). The threads at first consist of viscose, but when dried and submitted to treatment, which need not be described in detail, carbon bisulphide and alkali are eliminated and cellulose is formed. This is the most important process of artificial silk manufacture. Cellophane paper is also prepared in this way.

Artificial silks in which the thread is composed of cellulose are collectively known as *rayons*. All these varieties possess a high lustre and pure white colour, and may be obtained without difficulty in all shades by dyeing in the usual manner as for cotton. They have, however, a low tensile strength, especially in the moist state.

A material of different type is **cellulose acetate**. The spinning liquid is here a mixture of acetates formed by treating cellulose with acetic anhydride and acetic acid, with addition of either sulphuric acid or zinc chloride. The extent of acetylation is important. The triacetate is no use to manufacturers since it is insoluble and liable to attack. The desired degree of acetylation is $2\frac{1}{2}$ per glucose residue, the product then being soluble in acetone and capable of treatment in the usual spinning machinery. Acetate silk possesses a good lustre and great tenacity, and is insensitive to moisture, but is less readily dyed than rayon.

Cellulose acetate (*celanese acetate silk*) is non-inflammable and hence its use in the manufacture of moving picture films is preferable to that of the inflammable cellulose nitrate.

Cellulose Ethers

By the interaction of alkyl halides or sulphates with cellulose in the presence of alkali cellulose ethers are obtained, some of which are of great industrial importance owing to their stability and resistance to chemical attack, especially to alkalis. *Ethyl cellulose* and *benzyl cellulose* are the most important. In these products there is an average substitution of two hydroxyl groups per glucose unit.

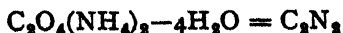
*Physical Properties of Substituted Cellulose Derivatives.*¹—It is held that the cellulose structure is made up of bundles of chains of β -glucopyranose units of diverse lengths which are held together by van der Waals forces and hydrogen bonds. The insolubility of cellulose in water is explained by the fact that the chains are packed together in such a way that the water molecules cannot break all the attractive forces at the same time and so force the chains apart, although large molecules such as diethyl-dibenzylammonium hydroxide may do this. One can also see why fully substituted celluloses such as the trinitrate or triacetate are insoluble in acetone (and therefore commercially useless) because the substitution is uniform and the packing is therefore good. When the substitution is no longer complete as in the cellulose acetate used for making acetate silk or the nitrate used for cordite (containing 2 to 2.5 substituent groups per glucose unit) so that some glucose units are fully substituted whereas others are only partially substituted, the packing of the chains is less precise and there are gaps into which the solvent can penetrate and the partially substituted material therefore dissolves. The same is true of the softening-points of cellulose ethers since the softening-point will depend on the forces of attraction between neighbouring chains. When these are high the softening-point, if it can be observed, will be high. Thus it is found that with the gradual etherification of the hydroxyl groups of cellulose by ethyl or benzyl residues, the softening point falls until it reaches a minimum. The degree of substitution at this point is between 2.0 and 2.5; as more alkyl groups are introduced, however, the softening-point rises again until complete substitution is reached. The point is further illustrated by the fact that benzyl celluloses have lower softening-points than the ethyl celluloses of the same degree of substitution which would be expected because of the greater size of the benzyl residue as compared with ethyl, thus causing greater interference with the attractive forces holding the long chains together.

XVIII

Cyanogen Compounds

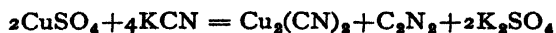
Cyanogen, C_2N_2 , was discovered in 1815 by Gay-Lussac. It is the first known example of a "compound radical" occurring unchanged throughout a whole series of derivatives, and playing in every case the part of a monovalent element. It behaves in many respects like the halogens, forming, for example, a hydrogen compound HCN , hydrocyanic acid, which strongly resembles the hydrogen halides in its properties.

Cyanogen, $\text{N}:\text{C}:\text{C}:\text{N}$, is the nitrile of oxalic acid and can be prepared from ammonium oxalate by heating it with dehydrating agents.



¹ *Chemistry of Large Molecules*, by E. Ott, p. 320.

Cyanogen is usually prepared by heating a solution of copper sulphate with potassium cyanide.



It is a colourless, very poisonous gas of pungent smell; it condenses to a liquid at -25° , and burns with a bluish-red flame.

Hydrogen cyanide, prussic acid, HCN, is found in the free state in certain tropical plants, and is formed from the glucoside *amygdalin*, by the hydrolytic action of the enzyme emulsin, both of these compounds being present in bitter almonds:



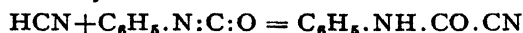
Hydrocyanic acid is best prepared by the action of concentrated sulphuric acid (diluted with an equal volume of water) upon a warm strong solution of sodium cyanide. Hydrogen cyanide escapes as a gas and can be condensed by use of a freezing mixture.

It is also manufactured in the United States by the dehydration of formamide.



It was originally prepared from Prussian blue, thus giving rise to the terms prussic acid and cyano-compound (from the Greek root signifying "blue").

In the anhydrous state hydrocyanic acid is a colourless liquid with a peculiar smell, reminiscent of bitter almonds. It boils at 26° , and solidifies to a crystalline mass at -14° . It is one of the weakest acids, and like most cyano-derivatives is exceedingly poisonous. Hydrocyanic acid readily combines with water, even on standing in solution, to form ammonium formate, from which it is easily regenerated by distillation. On reduction it yields methylamine, $\text{HCN} + 4\text{H} = \text{CH}_3.\text{NH}_2$. It unites directly with the carbonyl groups of aldehydes and ketones (see p. 187), and adds on to the double bond of ethylene derivatives. Phenyl isocyanate reacts with it to form cyano-formanilide.



The *constitution of hydrocyanic acid* as the nitrile of formic acid, H.C:N , is deduced from its production from ammonium formate and the ease with which it may be converted into the latter. It gives rise, however, to two distinct series of alkyl derivatives, namely, the cyanides R.C:N and the isocyanides R.N:C or R.N:C (see p. 228). The acid is generally classed as a liquid tautomeric compound, with the two forms HCN and HNC in equilibrium. Chemical evidence such as that given above in favour of one or other forms is far from convincing, but the Raman spectra show two bands, one strong corresponding to the nitrile frequency and one weak associated with the isonitrile frequency¹. The isocyanide form is calculated to be present only to 0.5 per cent.

¹ A. Dadieu, *Ber.*, 1931, 64, 358.

Potassium cyanide is used to remove silver salts in photography ; for the preparation of various double cyanides in electro-deposition ; and for the extraction of gold. The demand for potassium cyanide for these purposes has led to its preparation by leading ammonia or nitrogen over a red-hot mixture of charcoal and potassium carbonate. Potassium cyanate is first produced, which is then converted into potassium cyanide, probably as a result of the reducing action of the charcoal.

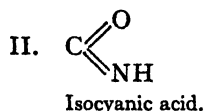
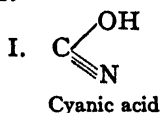


Potassium cyanide is obtained from the crude product by extraction with water, and salting it out of the concentrated solution by addition of potassium carbonate.

Alkyl derivatives of hydrogen cyanide, i.e. nitriles and isonitriles, have already been discussed in Chapter XI.

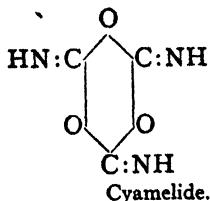
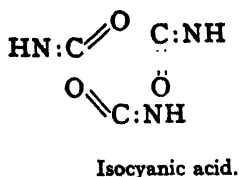
Cyanic Acid, Cyamelide, and Cyanuric Acid

Cyanic acid, HCNO , may be represented by either of the two possible structures I and II.



Only one cyanic acid, however, is known. This is obtained by the action of heat on cyanuric acid, and forms a colourless liquid which is unstable above 0°. As will be seen later, the acid is tautomeric, yielding derivatives corresponding to both of the types I and II.

At temperatures above 0° liquid cyanic acid is transformed with explosive violence into **cyamelide**, of the formula $(\text{CNOH})_3$. This is probably formed by the polymerisation of isocyanic acid, combination taking place between carbon and oxygen in the manner shown below. Cyamelide is a white, porcelain-like mass which is insoluble in water. On being heated it is depolymerised to cyanic acid. When heated with water the cyanic acid first produced decomposes slowly into ammonia and carbon dioxide.



Cyanuric acid, $(\text{CNOH})_3$, another polymeride of cyanic acid, was discovered long ago by Scheele during the dry distillation of urea, $\text{CO}(\text{NH}_2)_2$. Under the influence of heat the urea first breaks up into

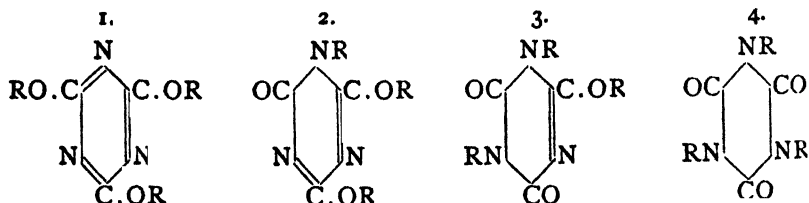
ammonia and cyanic acid, and the latter, by union between carbon and nitrogen, immediately polymerises to cyanuric acid :



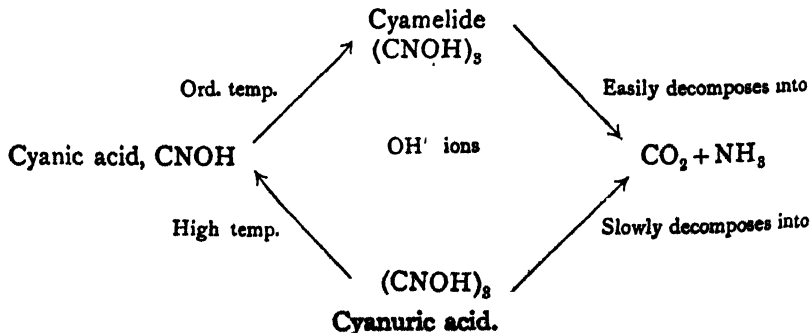
Cyanuric acid is also formed from cyanuric bromide (obtained by the action of bromine on potassium ferricyanide) by warming with water ; and by the isomerisation of cyamelide, which is effected slowly and partially on boiling with water, or more rapidly and completely with alkalis.

It is a tribasic acid which crystallises in rhombic prisms. On prolonged boiling with hydrochloric acid it decomposes into carbon dioxide and ammonia.

Cyanuric acid contains the radical $(\text{CN})_3$, in which carbon and nitrogen are linked alternately to form a closed ring. The solid acid is a tricarbimide of type 4 (below), and therefore a pseudo-acid. Hence it is known as pseudo-cyanuric or isocyanuric acid. The three pseudo-groups, CO.NH , are capable of isomerising into the salt-forming groups, C(OH):N , giving rise to four types of derivatives, as illustrated by the following formulæ of the isomeric *trialkyl esters of cyanuric acid* :



Cyanuric acid and cyamelide are therefore polymerides of cyanic acid possessing different constitutions. The relationship between these three compounds is illustrated in the following diagram (Hantzsch) :



Derivatives of Cyanic and Isocyanic Acids

A derivative of normal cyanic acid, $\text{HO.C}\equiv\text{N}$, is **cyanogen chloride**, $\text{Cl.C}\equiv\text{N}$, prepared by the action of chlorine on metallic cyanides or hydrocyanic acid, $\text{HCN} + \text{Cl}_2 = \text{NC.Cl} + \text{HCl}$. It is a very poisonous liquid which boils at 14.5° , readily polymerises to cyanuric chloride, $\text{C}_3\text{N}_3\text{Cl}_3$, and on treatment with potassium hydroxide yields potassium chloride and potassium cyanate.



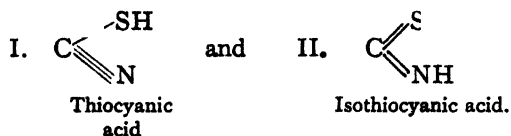
Esters of normal cyanic acid have not yet been isolated, but **isocyanic esters** O:C:NR , derived from the pseudo-acid are well known. The latter are obtained by heating salts of alkyl-sulphuric acids with potassium cyanate, or alkyl iodides with silver cyanate (cyanuric esters being also formed).



They are liquids of exceedingly pungent smell which boil without decomposition. When heated with alkali they decompose into carbon dioxide and primary amines. With ammonia and amines they unite to form derivatives of urea, $\text{C}_2\text{H}_5.\text{NCO} + \text{NH}_3 = \text{C}_2\text{H}_5.\text{NH.CO.NH}_2$, and with alcohol to form derivatives of carbamic acid. Esters of isocyanic acid gradually polymerise to cyanuric esters.

Thiocyanic Acid and Derivatives

Thiocyanic acid, *sulphocyanic acid*, HCNS , corresponds to cyanic acid, and like the latter may react in two forms :



Only one thiocyanic acid is known, which may be obtained by treating barium thiocyanate with an equivalent proportion of sulphuric acid, or dry mercury thiocyanate with gaseous hydrogen sulphide. It is a very volatile liquid with an acrid smell, and like cyanic acid readily passes into a solid polymeride. The free acid and its soluble salts give an intense red coloration with faintly acid solutions of ferric salts, a reaction used as a sensitive test for the ferric ion. The colour depends on the presence of the unionised compound, $\text{Fe}_2(\text{CNS})_6$.

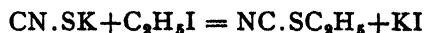
Potassium thiocyanate, CNSK , is obtained by fusing together potassium cyanide and sulphur. It dissolves readily in water with considerable absorption of heat. **Sodium thiocyanate** occurs in the saliva and urine of various animals. **Ammonium thiocyanate**, $\text{CNS}(\text{NH}_4)$, is prepared from carbon bisulphide and ammonia.



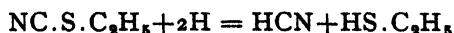
It forms deliquescent crystals, which on heating at 160° are transformed into thiourea, and at 180° into guanidine thiocyanate. **Silver thiocyanate**, CNSAg , is deposited as a precipitate resembling silver chloride during the volumetric estimation of silver by Volhard's method. **Mercury**

thiocyanate may be obtained as a grey amorphous precipitate; when moulded into pellets, dried and ignited, it forms long snake-like tubes of ash (Pharaoh's serpents).

Esters of normal thiocyanic acid, of the formula $\text{N} \equiv \text{C}-\text{S} \cdot \text{R}$, are obtained by heating potassium thiocyanate with potassium alkyl sulphates or alkyl iodides.

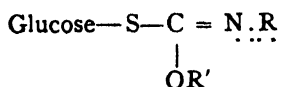


They are liquids smelling of garlic, and are insoluble in water. On reduction with zinc and sulphuric acid they yield hydrocyanic acid and mercaptans,

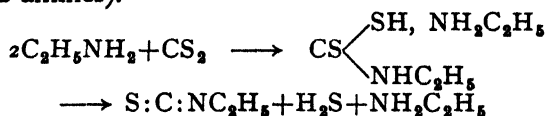


and when heated they partially isomerise into isothiocyanic esters.

The *esters of iso- or pseudo-thiocyanic acid*, $\text{S} : \text{C} : \text{N} \cdot \text{R}$, are known as mustard oils, and occur in various plants as glucosides of imino-thiocarbonic acid, of the type

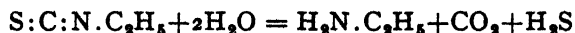


In addition to being formed by isomerisation of the normal esters, they are obtained by the action of mercuric or ferric chloride on amine salts of alkyl dithio-carbamic acids (prepared by the combination of carbon disulphide and amines).



They are lachrymatory liquids of extremely pungent odour, which are almost insoluble in water.

When heated to 100° with hydrochloric acid or to 200° with water they are hydrolysed to primary amines, carbon dioxide and hydrogen sulphide.



On reduction they are converted into a primary amine and thio-formaldehyde (trimeric).

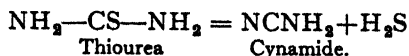


These reactions prove that in mustard oils the alkyl groups are linked to nitrogen.

The best known representative of this class is **allyl mustard oil** (*ordinary mustard oil*) $\text{S} : \text{C} : \text{N} \cdot \text{CH}_2 \cdot \text{CH} : \text{CH}_2$, which may be obtained from the seeds of black mustard (*Sinapis nigra*) by distillation with water. It is a colourless liquid, b.p. 148° , the vapour of which is exceedingly pungent and lachrymatory. The liquid raises blisters on the skin.

Cyanamide and Derivatives

Like carbide, **cyanamide** was discovered accidentally when the German chemists Frank and Caro in 1895 isolated it in an attempt to prepare metallic cyanides. It is formed from ammonia and cyanogen chloride, and also by treating thiourea with mercuric oxide or lead hydroxide.



Cyanamide is a colourless crystalline compound, which melts at 40° and readily polymerises. At 150° it is transformed into trimolecular *cyanuramide* or *melamine*, $\text{C}_3\text{N}_3(\text{NH}_2)_3$, which with formaldehyde forms resins sometimes superior to the urea-formaldehyde resins.

On the one hand it behaves as a weak base, and with strong acids forms salts which are hydrolysed by water. On the other hand it shows the properties of a weak acid, yielding metallic salts such as the technically important calcium cyanamide, and a yellow silver salt which is insoluble in ammonia.

Calcium cyanamide, CaCN_2 , is manufactured by passing nitrogen over calcium carbide in an electric furnace at 1000° C.

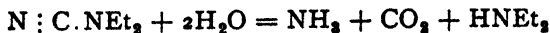


The product so obtained is extensively used as an artificial manure, as it decomposes slowly with water to give ammonia.

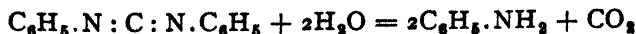


In this manner it is possible to prepare ammonia indirectly from atmospheric nitrogen, and the process is of great value from the agricultural point of view.

Cyanamide is probably an equilibrium mixture of the type $\text{N} : \text{C}.\text{NH}_2 \rightleftharpoons \text{NH} : \text{C} : \text{NH}$. The unsymmetrical formula is supported by the formation of cyanamide from cyanogen chloride and ammonia, $\text{CN}.\text{Cl} + \text{NH}_3 \longrightarrow \text{CN}.\text{NH}_2 + \text{HCl}$. Cyanamide yields two isomeric series of alkyl derivatives, pointing to an alternative structure. Diethylcyanamide on hydrolysis with acids decomposes into diethylamine, ammonia and carbon dioxide. It is therefore formulated as $\text{N} : \text{C}.\text{NEt}_2$.



The diphenyl derivative, diphenyl carbodiimide, on the other hand, yields under the same treatment aniline and carbon dioxide, and is assigned the symmetrical structure.



Tautomerism of this kind was early discovered among the amidines by von Pechmann.

Fulminic Acid

Fulminic acid, *carbonyl oxime*, $C:N.OH$, is regarded as the oxime of carbon monoxide, and possesses the properties of a strong acid. It is a very unstable, volatile compound, with a smell recalling that of hydrocyanic acid. Like the latter it is very poisonous. It is formed when fulminates are treated with strong acids and also by the decomposition of formamidoxime (isuretin).



Mercury fulminate, $(\text{CNO})_2\text{Hg}$, is the most important of the salts. It was discovered by Howard in 1799, and is largely used in percussion caps as a detonator for explosives. It is prepared technically by dissolving mercury in an excess of strong nitric acid, with the subsequent addition of alcohol. **Silver fulminate** may be obtained in a similar manner; it is much more explosive than the mercury compound, and is used in the manufacture of crackers.

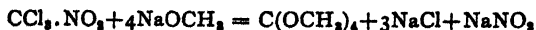
XIX

Derivatives of Carbonic Acid

Carbon dioxide is the anhydride of the very unstable carbonic acid, H_2CO_3 or O:C(OH)_2 , which may also be considered as hydroxy-formic acid, HO.COOH . Owing to the influence of the carbonyl group on the adjacent hydroxyl groups, the acid is dibasic. Carbonic acid and its salts are described in inorganic text-books, and only a few of its derivatives will be treated here.

I.—ESTERS AND ACID CHLORIDES OF CARBONIC ACID

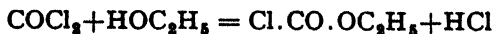
Esters of carbonic acid, CO(OR)_2 , are prepared by the action of alkyl iodides on silver carbonate, or of alcohols on carbonyl chloride, COCl_2 . They are ethereal smelling liquids and are soluble in water, in which they gradually decompose. *Esters of ortho-carbonic acid*, C(OR)_4 , are derived from the hypothetical ortho-carbonic acid, C(OH)_4 , and are formed by the action of sodium alcoholates on chloropicrin, $\text{CCl}_3.\text{NO}_2$. These are also ethereal smelling liquids.



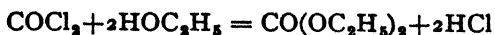
Carbonyl chloride, *phosgene*, COCl_2 , is produced by direct combination of carbon monoxide and chlorine at 100° in the presence of activated charcoal, or by exposing a mixture of gaseous chlorine and carbon monoxide to the direct rays of the sun.

Although a colourless gas at ordinary temperatures, carbonyl chloride readily condenses to a liquid of boiling-point 8° , in which form it is brought on to the market. It has a very penetrating, choking smell, readily dissolves in glacial acetic acid, benzene and other hydrocarbons, and

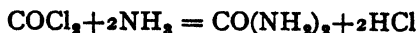
owing to the mobility of the chlorine atoms is very reactive. When heated with water it decomposes into carbon dioxide and hydrochloric acid, $\text{COCl}_2 + \text{H}_2\text{O} = \text{CO}_2 + 2\text{HCl}$. With alcohol the first product is *ethyl chloroformate*,



and finally *ethyl carbonate*

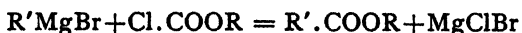


With ammonia it yields *urea*, the *diamide of carbonic acid*,



Phosgene is employed industrially in the preparation of di- and tri-phenylmethane dye-stuffs.

Chloro-formic esters, of the general formula Cl.CO.OR , are produced as mentioned above by the action of alcohols on phosgene. They are best obtained by adding the desired alcohol to strongly cooled liquid phosgene. They are volatile liquids of pungent smell, which are used for introducing the group $-\text{CO.OR}$ into organic compounds. With organo-magnesium halides they interact to give esters of carboxylic acids.



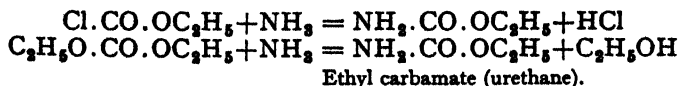
Ethyl chloroformate, $\text{Cl.COOC}_2\text{H}_5$, is a valuable synthetic reagent.

II.—AMIDES OF CARBONIC ACID

The dibasic nature of carbonic acid is also shown in the formation of two amides, viz., carbamic acid, a mono-amide, HO.CO.NH_2 , and urea, a diamide, $\text{CO}(\text{NH}_2)_2$. With these compounds should be grouped guanidine, $\text{C:NH}(\text{NH}_2)_2$.

Carbamic acid, HO.CO.NH_2 , is known only in the form of salts and esters. *Ammonium carbamate* is produced as a white mass by the combination of dry carbon dioxide and dry ammonia, $\text{CO}_2 + 2\text{NH}_3 = \text{CO}(\text{ONH}_2)(\text{NH}_2)$, and is present in commercial ammonium carbonate. On being warmed to 60° in aqueous solution it takes up a molecule of water and is converted into ammonium carbonate, $\text{CO}(\text{ONH}_2)(\text{NH}_2) + \text{H}_2\text{O} = \text{CO}(\text{ONH}_2)_2$.

Esters of carbamic acid are known as **urethanes**. They may be prepared by the action of ammonia on carbonic or chloro-carbonic esters at the ordinary temperature :



Ethyl carbamate (urethane).

also by heating acid azides with alcohols.

The urethanes crystallise well, distil without decomposition, and are soluble in alcohol, ether and water. With alkalis they decompose into carbon dioxide, ammonia and alcohols, and when heated with ammonia give urea.

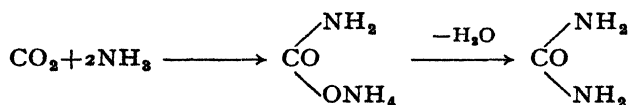
The compound commonly known as *urethane* is the ethyl ester of carbamic acid, $\text{H}_2\text{N.CO.OC}_2\text{H}_5$. It melts at 50° and boils at 184° .

When treated with very concentrated nitric acid it yields *nitro-urethane*, $\text{NO}_2 \cdot \text{NH} \cdot \text{CO} \cdot \text{OC}_2\text{H}_5$, from which nitramide was first isolated. Urethane is often employed as a narcotic in physiological experiments on the smaller animals.

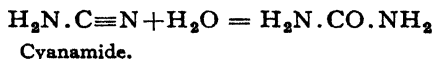
Trichloro-ethyl-urethane, $\text{H}_2\text{N} \cdot \text{CO} \cdot \text{OCH}_2 \cdot \text{CCl}_3$, is used as a hypnotic under the name of "Voluntal." Pharmacologically, it stands between chloral and urethane.

Urea, carbamide, $\text{NH}_2 \cdot \text{CO} \cdot \text{NH}_2$, the diamide of carbonic acid, was discovered in urine in 1773. It occurs in the urine of mammals and certain reptiles, and in many other liquids of animal origin. A human adult excretes about 30 gms. of urea per day, as the decomposition product of proteins.

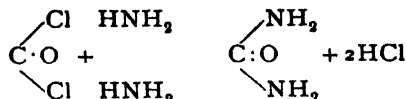
It is manufactured from ammonia and carbon dioxide which combine to give ammonium carbamate. This when heated at 200°C . under pressure loses water and forms urea.



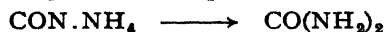
Another industrial method is the partial hydrolysis of cyanamide.



Synthetically, it is obtained by the action of ammonia on phosgene, ethyl carbonate, or urethane. These reactions prove the constitution of urea.



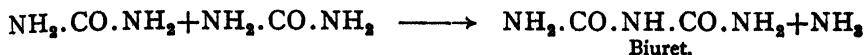
It is also formed by the intramolecular rearrangement of ammonium cyanate, when this is evaporated in aqueous solution :



This is the synthesis of urea effected by Wöhler in 1828, by evaporating an aqueous solution of potassium cyanate and ammonium sulphate. The potassium sulphate which crystallised out on cooling was filtered off and the filtrate evaporated to dryness. From the solid residue thus obtained urea can be extracted by means of alcohol.

Urea crystallises in long rhombic prisms or needles, which melt at 132° . It dissolves readily in water and alcohol but is practically insoluble in ether. Acids combine with urea to form salts, the most important being the *nitrate*, $\text{CON}_2\text{H}_4 \cdot \text{HNO}_3$, and *oxalate*, which are only sparingly soluble in water or nitric acid. Urea may therefore be precipitated from its solutions in these forms. Urea also yields salts with bases, and combines with certain salts to give crystalline addition compounds. It is used in the manufacture of resins, rubber accelerators, etc.

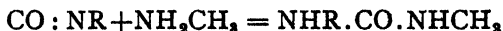
Like other acid amides, urea is readily hydrolysed on being heated with dilute acids or alkalis, or with water above 100° . This decomposition also occurs during the putrefaction of urine, $\text{CO}(\text{NH}_2)_2 + \text{H}_2\text{O} = \text{CO}_2 + 2\text{NH}_3$. When heated with pure thionyl chloride,¹ urea parts with ammonia and is converted into biuret.



Biuret forms colourless needles, melts in the anhydrous state at 190° , and gives a violet coloration with alkali and copper sulphate (*biuret reaction*). The reaction is characteristic not only of biuret but also of other substances such as the proteins which contain two or more $\text{NH}.\text{CO}$ groups in close proximity. With nitrous acid it reacts to give carbon dioxide, nitrogen and water, $\text{CO}(\text{NH}_2)_2 + \text{N}_2\text{O}_3 = \text{CO}_2 + 2\text{N}_2 + 2\text{H}_2\text{O}$. Nitrogen is also liberated by the action of sodium hypochlorite or hypobromite; the complicated reaction which occurs is used in the H \ddot{u} ffner method of estimating urea, by measuring the volume of the nitrogen evolved.

A much more convenient and accurate method of estimating urea depends on the action of *urease*, an enzyme occurring in soya beans. This converts urea quantitatively into ammonium carbonate, which can be determined directly by titration, or by liberating the ammonia with potassium carbonate and distilling it over into excess of standard acid.

Alkylated ureas, in which hydrogen is replaced by alkyl radicals, are known in considerable number. They are formed by various methods, e.g. when primary or secondary amines react with potassium cyanate or isocyanic esters.

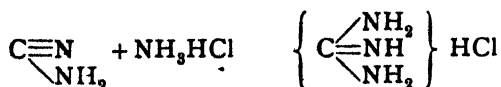


In their properties and reactions they strongly resemble urea.

Semicarbazide, $\text{NH}_2.\text{CO}.\text{NH}.\text{NH}_2$, is formed by the interaction of potassium cyanate and hydrazine hydrate. It is frequently utilised for the detection and isolation of aldehydes and ketones, since the condensation products, semicarbazones, obtained with these compounds usually crystallise well.

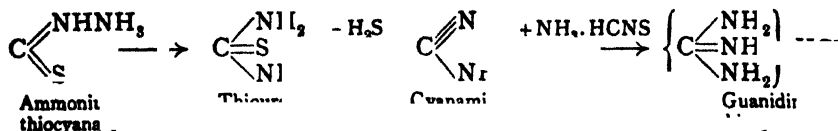


Guanidine, $\text{NH}:\text{C}(\text{NH}_2)_2$, may be regarded as imino-urea, or as the amidine of carbamic acid. It is contained in the seeds of the vetch and the juice of the sugar-beet, and is formed when cyanamide is heated with ammonium chloride solution.



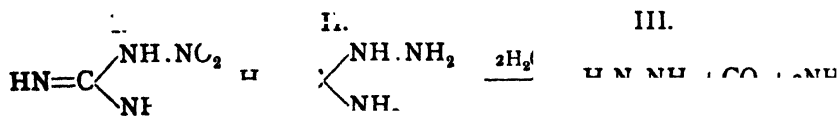
¹ R. C. Haworth and F. G. Mann, *J.*, 1943, 603.

Guanidine is generally prepared by heating ammonium thiocyanate at 180° to 190° , when cyanamide occurs as an intermediate product.



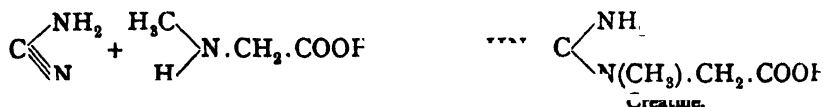
Guanidine is as strong a base as sodium hydroxide; is very soluble in water; and rapidly absorbs carbon dioxide from the air. It is generally obtained in the form of a salt such as the nitrate.

When guanidine is treated with a mixture of nitric and sulphuric acids it is converted into *nitro-guanidine* (I). This is the starting material for the preparation of a number of interesting derivatives of guanidine and urea. On reduction with zinc dust and acetic acid, nitro-guanidine yields *amino-guanidine* (II), which on boiling with acid decomposes into carbon dioxide, ammonia and *hydrazine* (III).

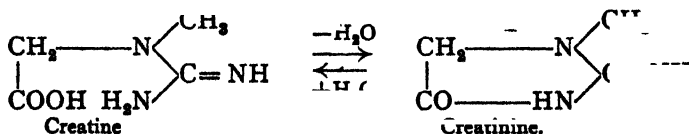


The hydrogen atoms in guanidine can be replaced by alkyl and other radicals. Important substitution products of this type are *arginine* (see p. 246), creatine and creatinine.

Creatine, *methyl-guanidyl-acetic acid*, was synthesised by Volhard from cyanamide and methylamino-acetic acid (sarcosine)



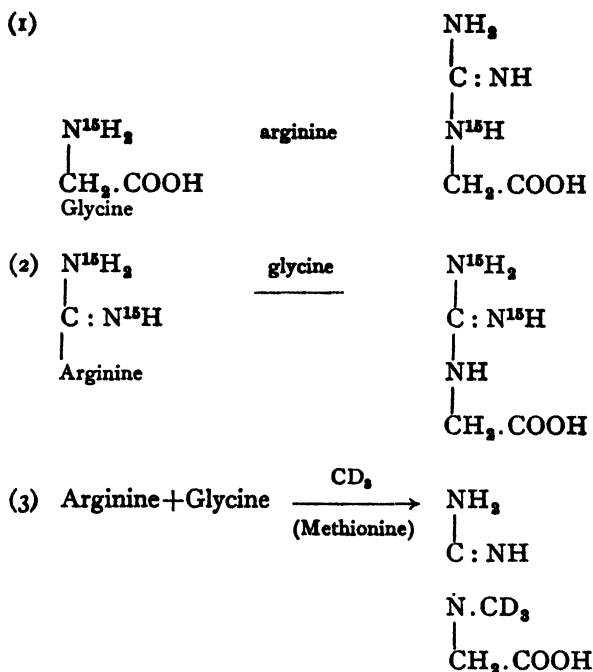
It was discovered by Chevreul in meat broth, and is present in muscle. Hence it can be prepared from extract of meat. Creatine is a crystalline compound of weak basic properties. It has a bitter saline taste. When warmed with dilute acids it loses water and yields creatinine.



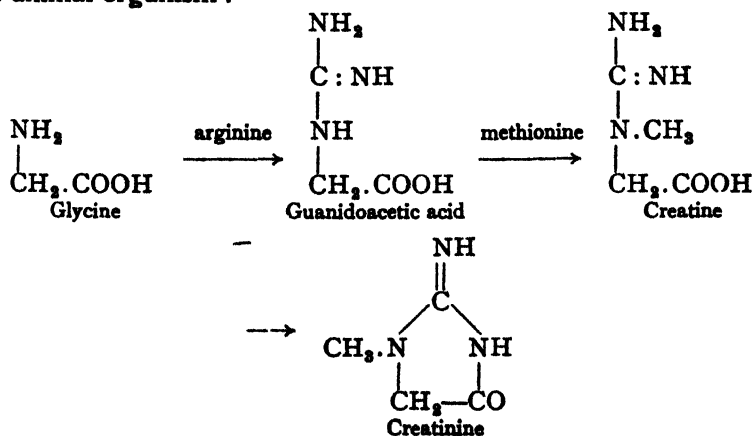
Creatinine is found in urine and in muscle. It is strongly basic. By combination with water it may be converted into creatine.

Deuterium and other isotopes have been employed with great success by Schoenheimer and others in the study of metabolic processes. As an example the synthesis of creatinine in the animal organism will be considered. When isotopic creatine is fed isotopic creatinine is excreted. It is therefore probable that creatine is the precursor of creatinine.

Moreover it was shown by the reactions represented below that creatine is formed from glycine by interaction with arginine the latter compound contributing the guanidyl group. The guanidoacetic acid so formed is then methylated by methionine.



The following is therefore the mechanism of the synthesis of creatine in the animal organism :—

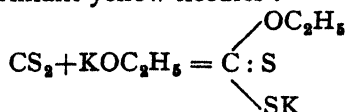


III.—SULPHUR DERIVATIVES OF CARBONIC ACID

Carbon disulphide, CS_2 , is prepared industrially by leading sulphur vapour over wood charcoal or coke at a red heat, and after fractionation is obtained as a colourless strongly-refracting liquid, b.p. 46° and sp. gr.

1.27. It has an unpleasant smell, a sharp taste, and is very inflammable, burning with a blue flame to give carbon dioxide and sulphur dioxide, $\text{CS}_2 + 3\text{O}_2 = \text{CO}_2 + 2\text{SO}_2$. Carbon disulphide is insoluble in water, but mixes in all proportions with alcohol and ether. It is a good solvent for iodine, sulphur, phosphorus, vegetable oils and resins.

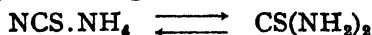
The following are the more important of its chemical reactions. Chlorine or bromine in the presence of a halogen "carrier" converts it into carbon tetrachloride or tetrabromide. On treatment with an alcoholic solution of potassium hydroxide it forms *potassium xanthate*, which crystallises in brilliant yellow needles :



Free *xanthic acids*, of the general formula $\text{RO} \cdot \text{CS} \cdot \text{SH}$, are very unstable. The name is derived from their property of giving *yellow* precipitates of cuprous xanthates with copper salts.

Carbon disulphide finds a number of uses. Owing to its great solvent power it is employed for extracting sulphur from sulphur ores and coal gas purification residues, and fats and oils from seeds, bones and other materials. It is also the starting material in the manufacture of potassium xanthate (used for destroying the vine louse), carbon tetrachloride, and cellulose xanthates (viscose, pp. 342 and 344).

Thiourea, *thiocarbamide*, $\text{NH}_2 \cdot \text{CS} \cdot \text{NH}_2$, is formed from ammonium thiocyanate by an intramolecular change similar to the urea transformation. In this case, however, the reaction takes place less readily (170° to 180°), and is also less complete, owing to the thiourea reverting to thiocyanate.



It is manufactured from calcium cyanamide and ammonium sulphide.

Thiourea crystallises in rhombic prisms, m.p. 172° , and dissolves readily in water or hot alcohol, but only sparingly in ether or cold alcohol. When boiled with acids or alkalis it decomposes into carbon dioxide, ammonia and hydrogen sulphide $\text{CS}(\text{NH}_2)_2 + 2\text{H}_2\text{O} = \text{CO}_2 + 2\text{NH}_3 + \text{H}_2\text{S}$. Like urea, it is a tautomeric substance, and may react according

to either of the formulæ $\text{NH}_2 \cdot \text{C} \begin{array}{l} \nearrow \text{NH}_2 \\ \searrow \text{S} \end{array}$ or $\text{HN} : \text{C} \begin{array}{l} \nearrow \text{NH}_2 \\ \searrow \text{SH} \end{array}$

XX

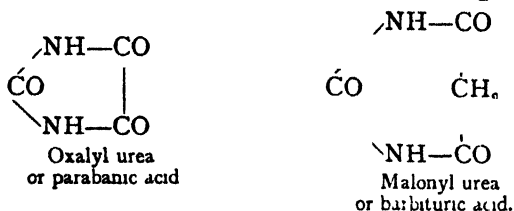
Ureides, Purines, and Nucleic Acids¹

Dibasic acids unite with urea in the same manner as with ammonia to form compounds of the amide type. When one carboxyl group alone enters into reaction, with loss of one molecule of water, the resulting

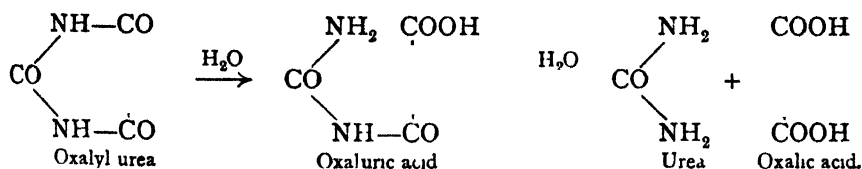
¹ *The Chemistry of Pyrimidines, Purines, and Nucleic Acids*, Treat B. Johnson in Gilman's *Organic Chemistry*, Vol. II, p. 948 (1938).

compounds are known as **ureido-acids**. If both carboxy groups take part, with elimination of two molecules of water, there are formed cyclic derivatives of urea known as **ureides**. Although these compounds are cyclic, the ring systems are comparatively easily opened. In addition, their properties and methods of formation are so closely related to those of open-chain products that they are more conveniently described at this stage than under the heading of heterocyclic compounds, where they properly belong. Of these two groups, the ureides are the more important, as they are closely related to a number of complex products such as uric acid, which occur in animal and vegetable organisms as a result of protein decomposition; others—uracil, thymine, and cytosine—are constituents of the nucleic acids (p. 373).

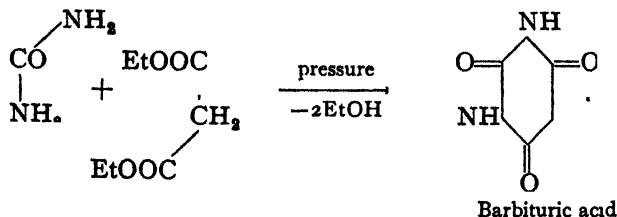
From the typical ureides, oxalyl urea and barbituric acid (malonyl urea), can be derived all the members of the uric acid group.



The ureides are for the most part beautifully crystalline compounds, the amide character of which is shown by the fact that on prolonged warming with dilute alkalis they take up two molecules of water to yield a dibasic acid and urea. Ureido-acids occur as intermediate products in this reaction.

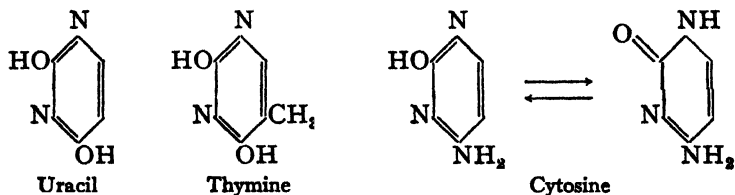


Barbituric acid is of special interest, as it was from one of its simple derivatives, pseudo-uric acid, that Fischer synthesised uric acid. It is prepared by the condensation of diethyl malonate with urea.



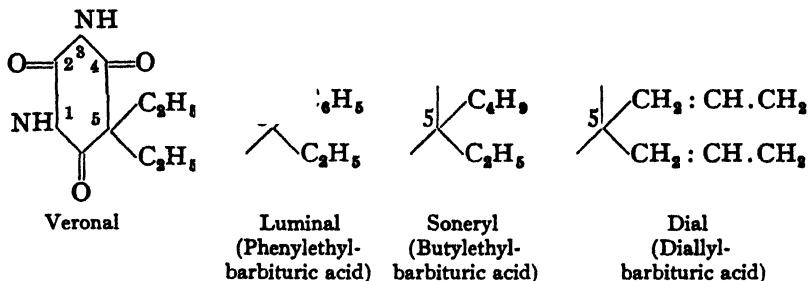
Barbituric acid is a pyrimidine derivative (p. 789) whose structure follows from its synthesis and from its oxidation to alloxan (p. 361). The methylene group in barbituric acid situated as it is between two carbonyl groups is extremely reactive.

Other simple derivatives of pyrimidine (p. 789) which are present in nucleic acids and are obtained from these by hydrolysis are *uracil*, *thymine*, and *cytosine*. Each contains a hydroxyl group in the 2-position and a hydroxyl or amino group in the 6-position. They exhibit lactam-lactim tautomerism.



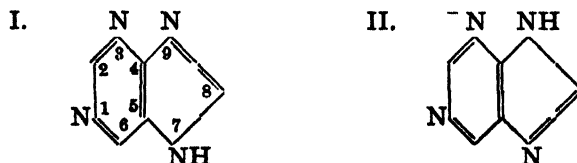
Veronal, *C-diethylbarbituric acid*, was shown by Fischer and Mehring (1903) to be an excellent hypnotic. It can be prepared by condensing the ester of diethylmalonic acid with urea in the presence of sodium ethoxide (*cf.* preparation of barbituric acid).

Veronal and other dialkylbarbituric acids—*luminal*, *soneryl*, *dial*, etc.—are among the most commonly used hypnotics.



Uric acid and other closely related compounds described here are termed **diureides**, as they contain two urea residues— $\text{NH}\cdot\text{CO}\cdot\text{NH}$ —in the molecule. All are derived from the same parent compound, which Fischer named **purine**.

The structure of purine may be represented by either of the two following formulæ:—

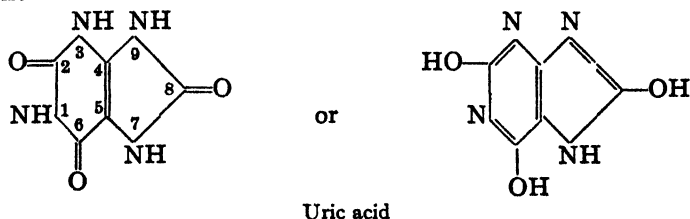


and we are, therefore, dealing with a case of tautomerism recalling that of the amidines. This peculiarity repeats itself in all these purine derivatives in which no oxygen is present in the five-membered ring. In the following pages formulæ of the type I will be adopted for purine and all related compounds, though the nucleotides (p. 370) are derivatives of type II.

The following summary shows the close relationship existing between a number of these compounds.

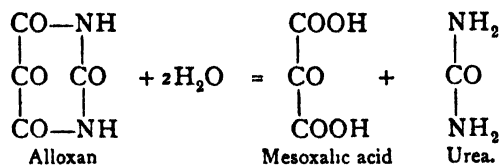
Uric acid, 2 : 6 : 8-*trihydroxypurine* $C_5H_4O_3N_4$, was discovered in 1776 by Scheele in urinary calculi and in human urine. It is found in the excrement of birds, and in particularly large quantities (25 per cent.) in the guano of the South Sea Islands ; it is also present in the excrement of snakes. Uric acid is the final product of purine metabolism in man, nucleoproteins being hydrolysed to purines which are then oxidised to the acid.

Uric acid is a white crystalline powder, very sparingly soluble in hot water, and practically insoluble in cold. As a weak dibasic acid it forms two series of salts, which are almost all difficultly soluble. The hydrogen atom in position 3 is the most strongly acidic, its replacement leading to the formation of acid salts. The atom in position 9 is next in acidic strength, and neutral urates are formed by replacement of these two atoms.

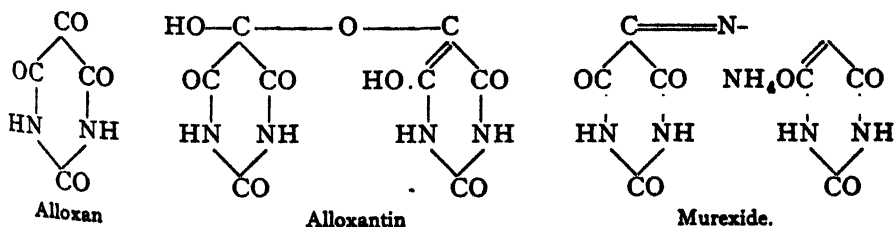


Structure of Uric Acid.—Uric acid is broken down most readily by oxidation, the products depending on whether the process is effected in acid or alkaline solution.

1. *Acid Oxidation.*—The chief products of the oxidation of uric acid by nitric acid are alloxan and urea ; consequently the atomic framework of the former compound must be present in uric acid.



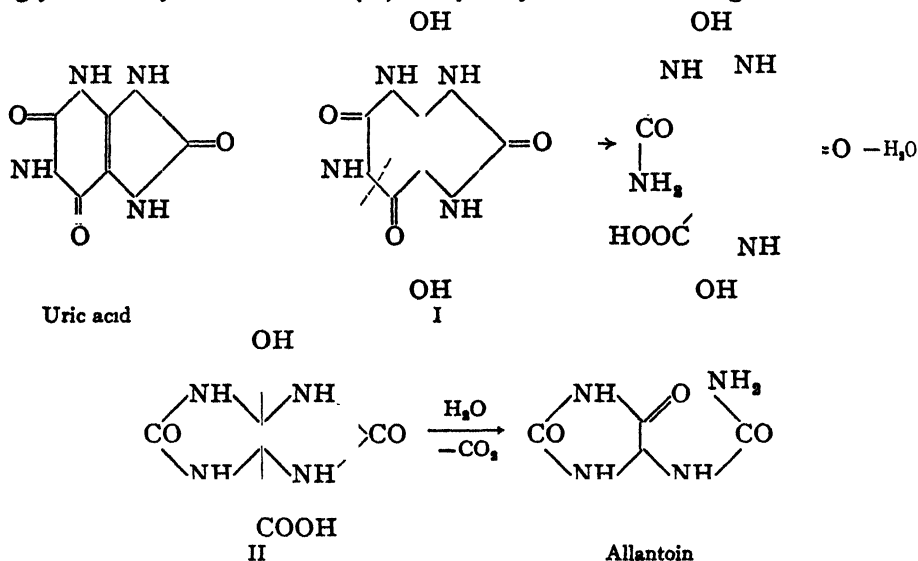
When dilute nitric acid is used to oxidise uric acid **alloxantin** is obtained. Various formulæ have been suggested for this compound, one of which is given.¹



¹ For other alloxantin and murexide formulæ see Treat B. Johnson, *Gilman's Organic Chemistry*, Vol. II., pp. 988 and 990 (1938).

Alloxantin with ammonia gives the ammonium salt of purpuric acid, *murexide*, which dissolves in water to give a purple solution. This is the basis of the *murexide test* for uric acid, which is carried out by adding a little dilute nitric acid to a few crystals of uric acid and carefully evaporating to dryness; the red residue becomes purple on the addition of ammonia, and blue with caustic soda.

2. *Alkaline Oxidation*.—Allantoin is the main product of the alkaline or neutral oxidation of uric acid. The most probable mechanism of the reaction is that of Robert Behrend,¹ who assumed that a glycol (I) was first formed, which was converted by hydrolysis and ring closure to glycoluriloxycarbonic acid (II). Hydrolysis of this acid gave allantoin.



That this is the correct interpretation was shown by the oxidation of methyluric acids: both 1-methyl- and 7-methyluric acids gave 3-methylallantoin, and 3-methyl- and 9-methyluric acids yielded 1-methylallantoin. The formulation of allantoin as the ureide of glyoxalic acid having the structure shown is based on its synthesis from glyoxalic acid and urea.

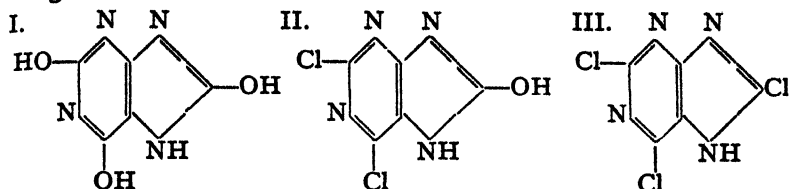
Allantoin, m.p. 238°-240°, occurs in human urine in very small quantities, but in other mammals is the chief product of purine metabolism.

These reactions and several syntheses confirm the above formula for uric acid, which may, however, exist in two tautomeric forms (pp. 361-363). Absorption spectra measurements show that the carbonyl form predominates. With phosphorus oxychloride uric acid, however, reacts in the tautomeric form (I), being converted first into 2:6-dichloro-8-hydroxy-purine (II), and finally at higher temperatures into 2:6:8-trichloro-purine (III).

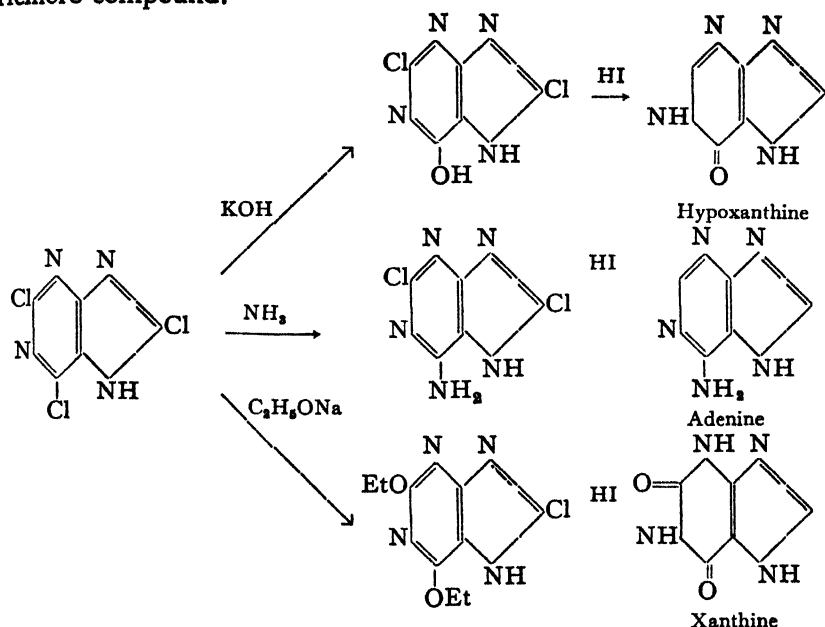
These chloro-compounds, and particularly 2:6:8-trichloro-purine, are of great importance for the synthesis of other purine derivatives

¹ Behrend and Grünwald, *Ann.*, 1902, 323, 180.

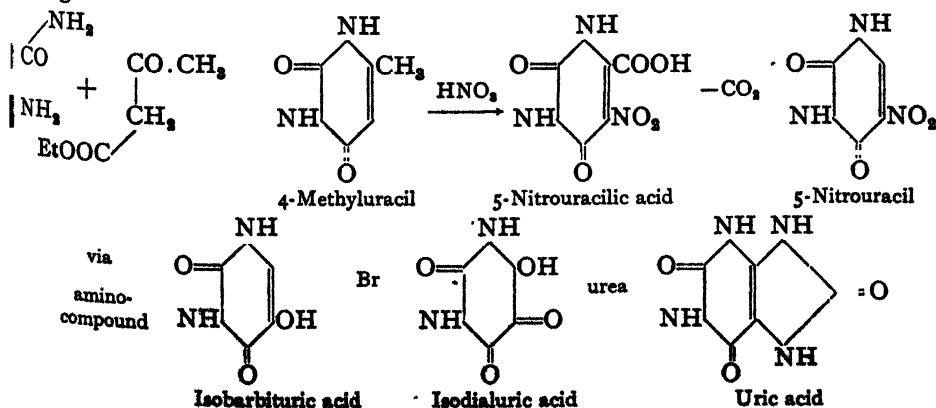
from the comparatively cheap uric acid. For example, Fischer by making use of the different reactivities of the chlorine atoms—



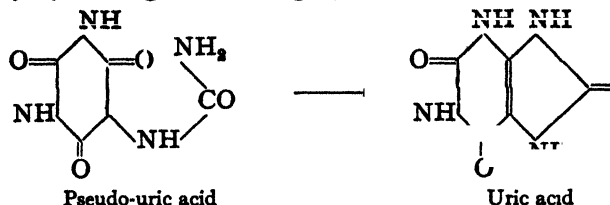
position 6 > position 2 > position 8—was able to prepare xanthine, adenine, guanine, and hypoxanthine as well as purine itself from the trichloro-compound.



Synthesis of Uric Acid.—1. The first decisive synthesis of uric acid was effected in 1889 by Behrend and Roosen, in the following stages.

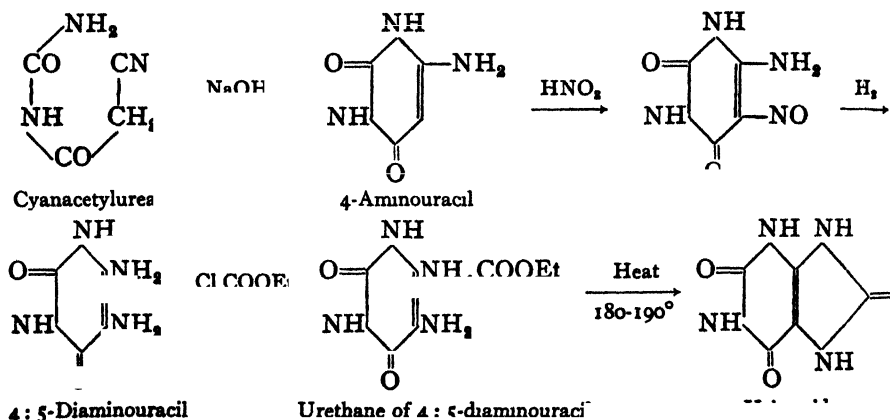


2. The next and simplest synthesis of uric acid was carried out by Fischer and Ach in 1895. This depends on the removal of the element of water from pseudo-uric acid by fusion with oxalic acid, or more conveniently by boiling with strong hydrochloric acid.



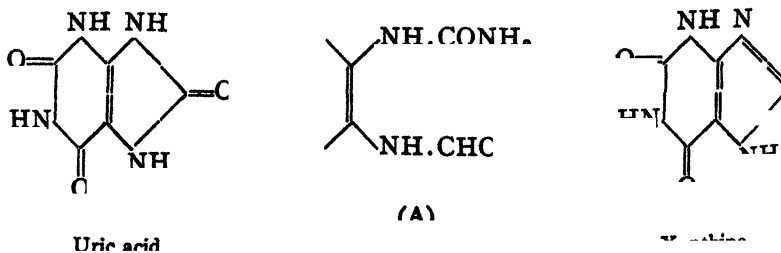
As pseudo-uric acid is obtained from violuric acid, the oxime of alloxan, this synthesis permits the reconstruction of the uric acid molecule from its chief oxidation product, alloxan. Further, by starting from methyl alloxan and dimethyl alloxan there can be obtained methyl pseudo-uric acids, from which it is possible to prepare methylated uric acids.

3. A synthesis of general application and hence of great preparative value is that due to Traube. It makes use of cyanacetyl urea, formed by condensing cyanacetic acid with urea (formula below).



By utilising the alkyl derivatives of urea this synthesis may be employed for the preparation of alkylated uric acids.

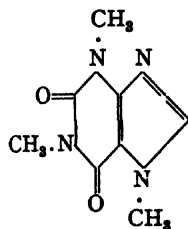
Xanthine, 2:6-dihydroxy-purine is prepared quantitatively by heating uric acid with formamide.¹ The intermediate A is probably formed



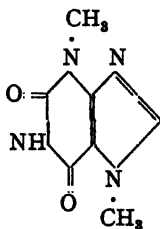
¹ H. Bredereck, H-G. Von Schuh, and A. Martini. *Ber.*, 1950, 83, 201.

which loses carbon dioxide and ammonia to give xanthine. It may also be obtained synthetically from 2:6:8-trichloro-purine (see p. 363) or by the action of potassium hypobromite on glyoxaline-4:5-dicarboxy-amide.¹ Xanthine is a normal constituent of many animal tissues and is formed from guanine by treatment with nitrous acid. Under specified conditions it yields theobromine and caffeine in good yield when treated with dimethyl sulphate.

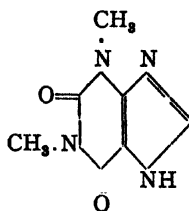
Caffeine.—The most important of the five naturally occurring methyl derivatives of xanthine is caffeine, 1:3:7-trimethyl-2:6-dihydroxy-purine. It is the component of tea and coffee responsible for the stimulating action of these beverages on the nerves and heart, and for that reason is employed in medicine. It crystallises in silky needles and melts at 236°. It is manufactured from theobromine by methylation with dimethyl sulphate in alkaline solution.



Caffeine
(1:3:7-Trimethylxanthine)



Theobromine
(3:7-Dimethylxanthine)

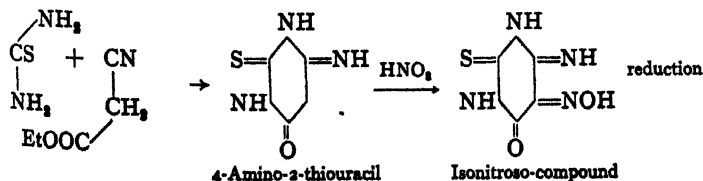


Theophylline
(1:3-Dimethylxanthine)

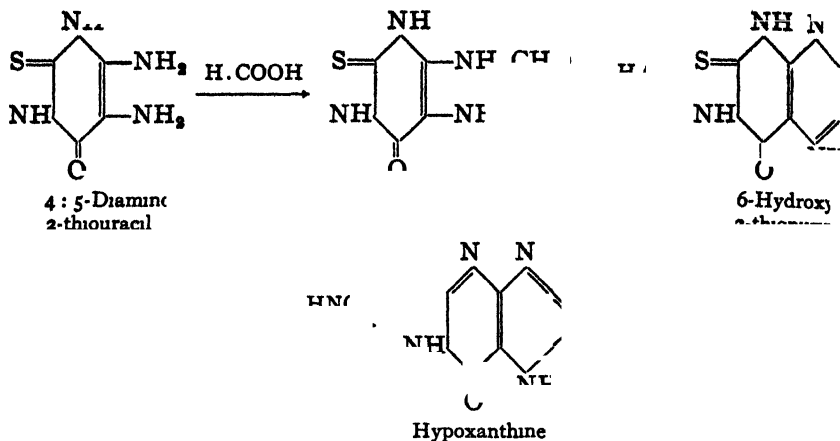
Theobromine, 3:7-dimethyl-xanthine, is closely allied to caffeine and occurs in cocoa (1 or 2 per cent.). It is a white crystalline compound m.p. 351°, and is employed as a diuretic. Its structure has been shown by synthesis from 3:7-dimethyluric acid.

Theophylline, 1:3-dimethyl-xanthine, is isomeric with theobromine and has been found in tea. The anhydrous compound melts at 264°, and its diuretic action surpasses theobromine. It is prepared on the technical scale from dimethylurea and cyanacetic acid by a modification of Traube's method (*cf.* p. 365).

Hypoxanthine, *sarkine*, 6-hydroxy-purine (formula, p. 363), is frequently found associated with xanthine in the animal organism, and is present in muscles, spleen, liver, and pancreas. It is a crystalline powder of basic character, which decomposes at 150°. It may be prepared from 2:6:8-trichloro-purine (p. 363). It has also been synthesised from cyanacetic ester and thiourea in the following stages:—



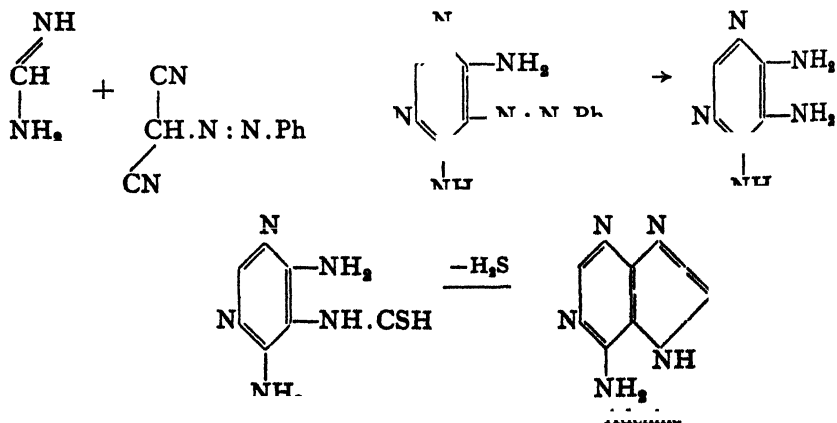
¹ R. A. Baxter and F. S. Spring, *Nature*, 1944, 254, 462. *J.*, 1945, 232.



Whereas the hydroxy-purines, *uric acid*, *hypoxanthine*, and *xanthine*, are formed in the animal organism as intermediate or final product of metabolism with a view to subsequent elimination from the system the amino-purines, *guanine* and *adenine*, are essential constituents of the important nucleic acids, and must be regarded as indispensable for the life processes of the cell.

Guanine, *2-amino-6-hydroxy-purine* occurs in the pancreas of certain animals and is present in large amounts in guano. It is prepared from cyanacetic ester and guanidine. When treated with nitrous acid it is converted into xanthine.

Adenine, *6-amino-purine* (formula below), is formed along with guanine when nucleic acids are hydrolysed. It has been prepared by the action of ammonia on trichloro-purine. It has been obtained in good yield from formamidine and benzeneazomalononitrile¹ :—



When treated with nitrous acid, adenine is converted into 6-hydroxy-purine or hypoxanthine.

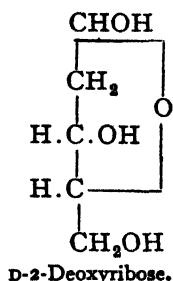
¹ I. Baddiley, B. Lythgoe and A. R. Todd, *J.*, 1943, 186.

Nucleosides

Purines or pyrimidines condense with pentoses to form *nucleosides* examples of which are given in the following table.

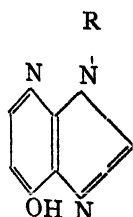
Base	Pentose	Nucleoside
Adenine	D-Ribose	Adenosine
Guanine	D-Ribose	Guanosine
Cytosine	D-Ribose	Cytidine
Xanthine	D-Ribose	Xanthosine
Uracil	D-Ribose	Uridine
Hypoxanthine	D-Ribose	Inosine
Thymine	2-D-Deoxyribose	Thymidine

Many of the nucleosides are obtained as crystalline substances from nucleic acids by partial hydrolysis. On hydrolysis they yield a base (a purine or pyrimidine) and a pentose (D-ribose or D-deoxyribose). They

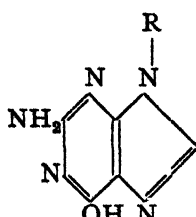


are glycosides since they have no reducing properties and this has been confirmed by hydrolysis with dilute hydrochloric acid.

Further investigation has shown that the pentose is linked to the N_3 of the pyrimidine ring and to the N_9 of the purine ring. The methods used to establish the point of attachment may be illustrated by two examples. (1) Uridine on methylation yields an N-methyluridine which on hydrolysis gives N_1 -methyluracil. It follows that in uridine the ribose is attached to the N_3 atom. (2) Chemical evidence indicates that in the purine nucleosides the pentose groups must occupy either position 7 or 9 in the purine molecule.¹ A decision between the two positions was



(R = Ribose residue)
9-Methylxanthine
(R = Methyl)

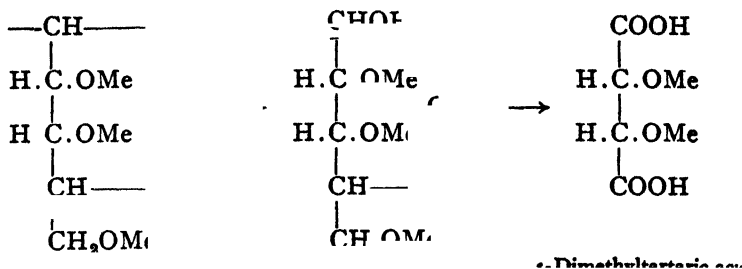


(R = Ribose residue, CH_2OH)
9-Methylguanine
(R = Methyl)

¹ J. M. Gulland and T. F. Macrae, *J.*, 1933, 662.

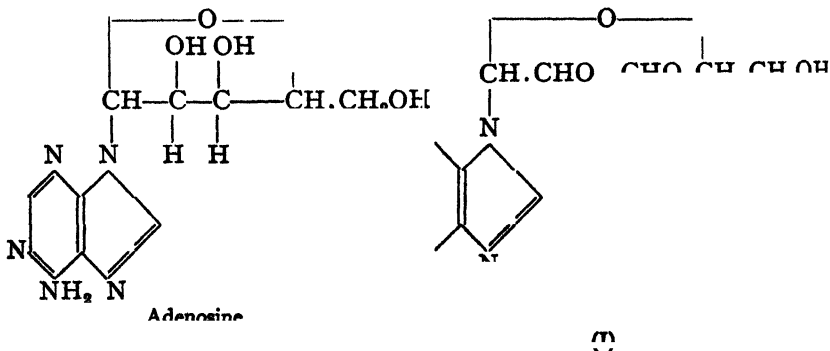
made by means of ultra-violet absorption spectra which show that the glycosidic linkage occurs at position 9, since the spectra of xanthosine (deaminated guanosine) closely resembles that of 9-methylxanthine but not that of 7-methylxanthine : ¹ a similar result is obtained with guanosine, 7- and 9-methylguanines.²

The ribose molecule is shown to have the furanose structure, since guanosine when methylated with dimethyl sulphate and alkali and then hydrolysed gives a methylated sugar which can be oxidised to *meso*-



dimethyltartaric acid. A pyranose structure would have resulted in the formation of a trimethoxyglutaric acid. It follows that guanosine has the structure given in the formula.

Periodate oxidation has furnished further valuable information about the constitution of the purine nucleosides. Adenosine on periodate oxidation gives a dialdehyde (I) whose constitution was proved synthetically³ by the oxidation of 9-D-mannopyranosidoadenine. In adenosine



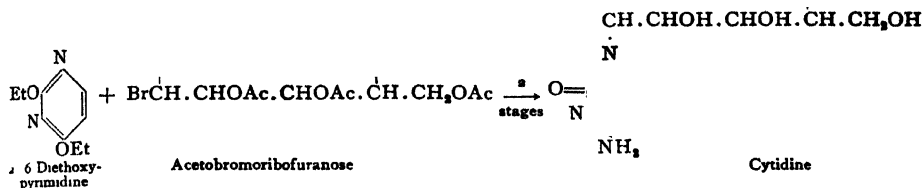
therefore, the ribose is attached to the adenine residue at N₉. The same dialdehyde was also obtained from a glucosidyl adenine to which a β -configuration had been assigned with fair certainty. Adenosine in consequence is a β -glycoside.

Confirmation of the above conclusions has come from two other sources. X-ray analysis has supplied further evidence that the structures assigned to the nucleosides as the result of chemical investigations are

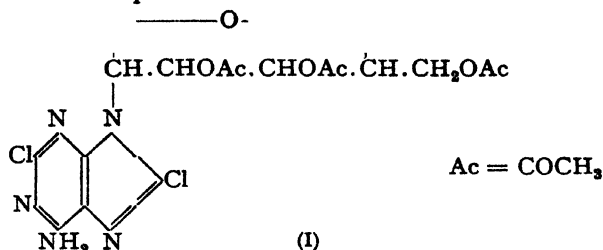
¹ J. M. Gulland, E. R. Holiday and T. F. Macrae, *J.*, 1934, 1639. ² J. M. Gulland and L. F. Story, *J.*, 1938, 692. ³ B. Lythgoe, H. Smith and A. R. Todd, *J.*, 1947, 355.

correct. For instance, cytidine has been shown to be cytosine-3- β -D-ribofuranoside.¹

Final confirmation comes from the synthetic work of Todd² and his collaborators at Cambridge. The first synthesis of a naturally occurring nucleoside was accomplished when cytidine was synthesised. 2:6-Diethoxypyrimidine and acetobromoribofuranoside give an intermediate substance which with methanolic ammonia exchanges the 6-ethoxy group for an amino group and hydrolyses the acetyl groups to give cytidine. This also constitutes a synthesis of uridine.

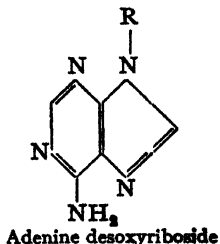
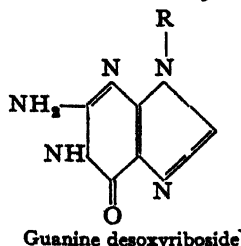


Adenosine has been synthesised³ by condensing 2:8-dichloroadenine with acetochlororibofuranose to give the product I. The acetyl groups and chlorine atoms were replaced by hydrogen by hydrolysis and hydrogenation respectively to give adenosine. Guanosine has been synthesised by a somewhat similar procedure.⁴



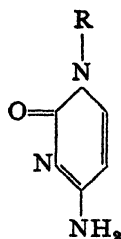
The nucleosides from thymonucleic acid are deoxyribosides of guanine, adenine, cytosine, and thymine, with the pyrimidine or purine attached to the sugar residue through the N₃ or N₉ positions respectively.

Nucleosides from Thymonucleic Acid

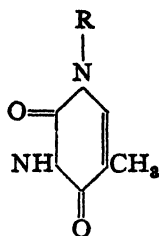


¹ S. Furberg, *Acta Chem. Scand.*, 1950, 4, 751. ² G. A. Howard, B. Lythgoe and A. R. Todd, *J.*, 1947, 1052. ³ J. Davoll, B. Lythgoe and A. R. Todd, *J.*, 1948, 947. ⁴ J. Davoll, B. Lythgoe and A. R. Todd, *J.*, 1948, 1685.

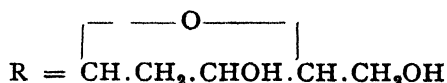
NUCLEOTIDES



Cytosine desoxyribose



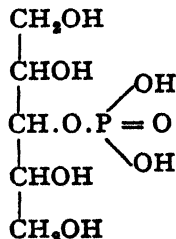
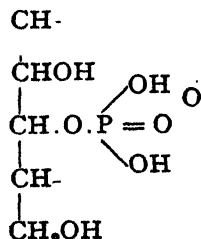
Thymine desoxyribose

Nucleotides¹

Important derivatives of the nucleosides are their phosphates, the *nucleotides*, which are obtained by the controlled hydrolysis of nucleic acids (see p. 374). For example, cold alkaline or enzymatic hydrolysis of yeast nucleic acid yields the four nucleotides: *adenylic acid*, *guanylic acid*, *cytidylic acid*, and *uridylic acid*. The nucleotides when hydrolysed in neutral solution afford nucleosides and phosphoric acid, thereby showing that they are the phosphoric esters of the nucleosides. The four nucleotides mentioned above thus give adenosine, guanosine, cytidine, and uridine respectively. It is also possible to hydrolyse nucleotides to D-ribose phosphoric acid, from which it follows that the phosphate group is attached to the ribose. The nucleotides therefore possess the structure.

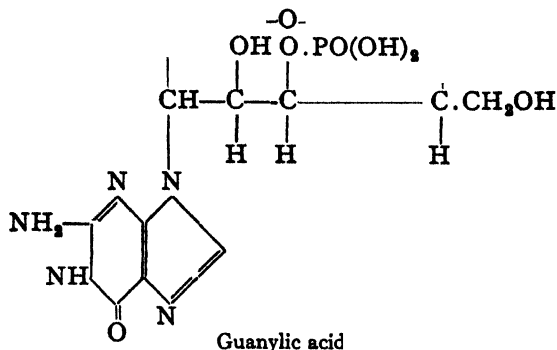
Base—Pentose—Phosphoric acid

The point of attachment of the phosphate to the pentose was ascertained by deaminating *guanylic acid* to give *xanthylic acid*, which is hydrolysed in aqueous solution to xanthine and D-ribose phosphate. The ribose phosphate on catalytic reduction yields a ribitol phosphate which is optically inactive thus showing that the phosphate group occupies the symmetrical 3-position.

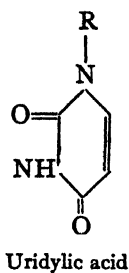
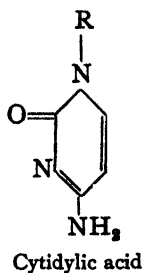
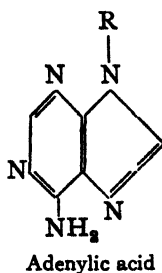


¹ B. Lythgoe, "Chemistry of the Adenine Nucleotide Coenzymes," *Ann. Reports*, 1945, 42, 175. "Chemistry of Nucleosides and Nucleotides," *ibid.*, 1944, 41, 200.

As a result of these and other methods guanylic acid was assigned the following formula :



Adenylic acid, cytidylic acid, and uridylic acid were likewise regarded as adenosine-, cytidine-, and uridine-3'-phosphates respectively.

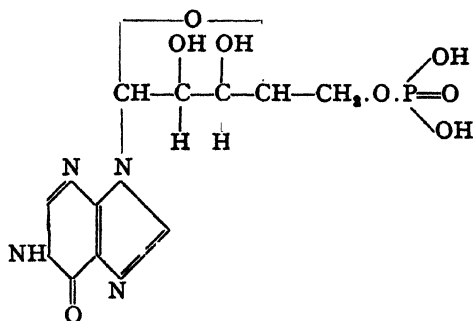


A complicating factor, however, arises from the recent observation that the nucleotides obtained from the alkaline hydrolysis of yeast ribonucleic acid are mixtures, *e.g.* adenylic acid *a* and *b*.¹ This result is due to the ease with which phosphoryl migration occurs between the 2'- and 3'-positions in the nucleotides. It is now known that adenylic acid *a* is adenosine-2'-phosphate and adenylic acid *b* the 3'-phosphate.²

In muscle a nucleotide occurs which is an adenosine phosphate, but which differs from yeast adenylic acid. It is termed *muscle adenylic acid* and is most conveniently prepared by synthesis. It is also obtained by the hydrolysis of adenosine triphosphate (p. 372). It is converted by nitrous acid or enzymatically to inosinic acid (p. 372). It is therefore adenosine-5' phosphate and this has been confirmed by periodate oxidation³ and by synthesis.⁴

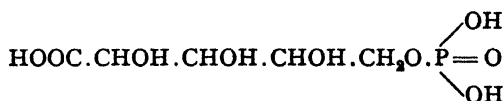
¹ W. E. Cohn, *J.A.C.S.*, 1950, **72**, 2811. H. C. Loring, N. G. Luthy, H. W. Bortner and L. W. Levy, *ibid.*, 1950, **72**, 2811. ² D. M. Brown and A. R. Todd, *J.*, 1952, **44**. *Nature*, 1953, **172**, 1184. J. J. Fox, L. F. Cavaliere and N. Chang, *J.A.C.S.*, 1953, **75**, 4315. D. M. Brown, G. D. Fasman, D. I. Magrath, and A. R. Todd, *J.*, 1954, 1448. ³ J. Baddiley, G. W. Kenner, B. Lythgoe and A. R. Todd, *J.*, 1944, 657. ⁴ J. Baddiley and A. R. Todd, *J.*, 1947, 648.

A nucleotide of interest is *inosinic acid*, which was isolated in the crystalline form from meat by Liebig.



Inosinic acid

When heated with 1 per cent. aqueous hydrochloric acid, the purine residue is detached leaving a ribose phosphate which was shown to be D-ribofuranose-5 phosphate by its conversion into phosphoribonic acid (see formula) on oxidation with nitric acid.



Phospho-ribonic acid

Under this treatment any of the isomeric pyranose ribose phosphates would have produced a phospho-trihydroxyglutaric acid. Alkaline hydrolysis of inosinic acid yields the nucleoside *inosine* (hypoxanthine 9-β-D-ribofuranoside).

Nucleotides have been found which are not components of nucleic acids, but which have important coenzyme functions. Of outstanding importance among these is *adenosine-5' triphosphate* (ATP) which was

Nucleotide Coenzymes

R = H Adenosine

CH.CHOH.CHOH.CH.CH₂OR R = PO(OH)₂ Muscle adenylic :



R = $\begin{array}{c} \text{O} \\ \parallel \\ \text{P} - \text{O} - \text{PO}(\text{OH})_2 \\ | \\ \text{OH} \end{array}$ Adenosine diphosphate

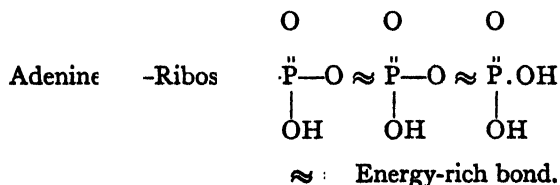
R = $\begin{array}{c} \text{O} \quad \text{O} \quad \text{O} \\ \parallel \quad \parallel \quad \parallel \\ \text{P} - \text{O} - \text{P} - \text{O} - \text{P}(\text{OH})_2 \\ | \quad | \quad | \\ \text{OH} \quad \text{OH} \quad \text{OH} \end{array}$ Adenosine triphosphate

isolated from muscle by K. Lohmann in 1929. On hydrolysis with

dilute alkali it yields muscle adenylic acid and inorganic pyrophosphate, and with dilute acid one molecule gives adenine (1 mol.), pyrophosphoric acid (2 mol.) and D-ribose-5-phosphate. Since the structure of muscle adenylic acid is known (see above), the structure of adenosine triphosphate is known with the exception of the position of two phosphoryl groups. Lohmann proposed the formula given above since it satisfied the observation that adenosine triphosphate contains three primary and one secondary acidic grouping. The correctness of this formulation was established by Lythgoe and Todd¹ by periodate oxidation and synthesis.²

It is possible to remove only one phosphoryl group from adenosine-5' triphosphate to give *adenosine-5' diphosphate* (ADP). The formula given above satisfies the condition that adenosine diphosphate contains two primary and one secondary acidic group. It has been confirmed by synthesis.³

Adenosine triphosphate and adenosine diphosphate occur both in plant and animal cells and play an important role in carbohydrate metabolism and fermentation (p. 336). They are coenzymes and function in phosphate transfer reactions (*transphosphorylations*). A full understanding of these processes became possible only when Lipmann discovered that adenosine di- and tri-phosphates contain so-called *energy-rich phosphate bonds*. Lipmann showed that when two phosphate groups which are linked together undergo hydrolysis an unusually great loss of free energy occurs. It follows that certain reactions which involve an increase in free energy can take place provided they occur simultaneously with a dephosphorylation such as the conversion of adenosine triphosphate to adenosine diphosphate.



Other substances containing energy-rich phosphate bonds are 1:3-diphosphoglyceric acid and phospho-enol pyruvic acid.

Nucleic Acids ⁴

The nucleic acids are colourless, amorphous compounds containing carbon, hydrogen, oxygen, nitrogen, and phosphorus. They are

¹ *Nature*, 1945, 155, 695. ² J. Baddiley, A. M. Michelson and A. R. Todd, *J.*, 1949, 582.
³ J. Baddiley and A. R. Todd, *J.*, 1947, 648. ⁴ "The Biochemistry of the Nucleic Acids,"
 J. N. Davidson (Methuen and Co. Ltd., 1956). "Nucleic Acids, Nucleosides and Nucleotides,"
 J. Baddiley, *Ann. Reports*, 1950, 47, 253. J. M. Gulland, G. R. Barker and D. O. Jordan,
 "Nucleic Acids and Nucleoproteins," *Ann. Rev. Biochem.*, 1945, 14, 175. E. J. Bourne, *Ann. Reports*, 1952, 49, 246.

macro-molecules of high molecular weight—frequently as great as 500,000 or 1,000,000—and when broken down by hydrolysis yield nucleotides (see p. 370). The nucleic acids therefore are **polynucleotides**.

The nucleic acids are generally divided into two main groups, according to the pentose present. The *ribonucleic acids*, of which *yeast nucleic acid* is an outstanding example, contain D-ribose and are of cytoplasmic origin. The *deoxyribonucleic acids* such as *thymonucleic acid* contain D-deoxyribose, and occur in cell nuclei. Both types probably occur in every living tissue.

According to the method of treatment the nucleic acids undergo partial or complete hydrolysis, and the products have been intensively studied especially in recent years by Levene, Gulland, and Todd. Partial hydrolysis yields, as stated above, nucleotides. Complete hydrolysis with dilute mineral acids results in the formation of phosphoric acid, purine or pyrimidine bases, and pentoses (or furfural formed from them). As will be seen from the following table, yeast nucleic acid differs from thymonucleic acid by having uracil in place of thymine and D-ribose instead of D-2-deoxyribose.

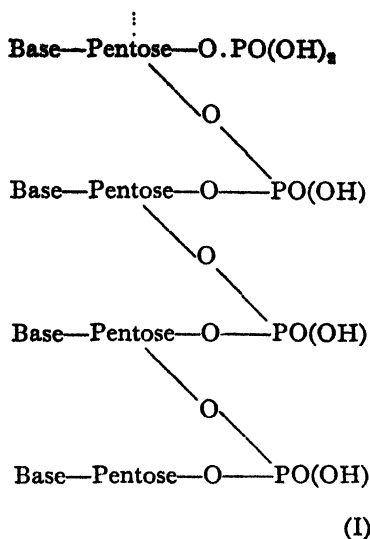
Hydrolysis Products.

Yeast Nucleic Acid.	Thymonucleic Acid.
Adenine	Adenine
Guanine	Guanine
Cytosine	Cytosine
Uracil	Thymine
D-Ribose	D-2-Desoxyribose
Phosphoric acid	Phosphoric acid

Another base, 5-methylcytosine, has been found to be a minor constituent of deoxypentosenucleic acids.

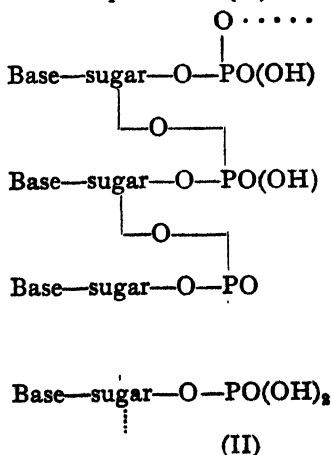
Insight into the manner in which these constituents are linked to one another is obtained by a study of the nucleotides and nucleosides, which as already stated are obtained by the partial hydrolysis of nucleic acids. With the chemistry of the nucleosides and the nucleotides almost completely understood there remains the problem of the order of the nucleotides and their mode of combination in the nucleic acid, as well as the structure of the resulting long-chain molecules.

The structure of the nucleic acids raises problems similar to those of other macromolecules; *e.g.* are the chains straight or branched; how are the nucleotide units arranged, etc.? These questions have only been partially answered. The building stones of the nucleic acids are undoubtedly nucleotides, and since each nucleic acid yields four different nucleotides it was at first concluded that the nucleic acid molecule is a tetranucleotide, an example of which is that suggested by Levene and Simms and given in (I).



This, however, is a gross oversimplification. The molecular weights assigned to the nucleic acids are now very much higher than was previously estimated. In other words, the nucleic acids are *polynucleotides* and not tetranucleotides. The macromolecules might, of course, be composed of tetranucleotide units, each unit containing a molecule of adenine, guanine, cytosine, and uracil. This likewise is incorrect since recent workers¹ have found that in yeast ribonucleic acid the four bases are not present in equimolecular quantities. In one sample the bases were found to occur in the following molar proportions: adenine (3.2), guanine (3.1), cytosine (3.0), and uracil (1.0).

A further refinement was necessary when it was found by careful electrometric titrations that for every 4 phosphorus atoms in yeast nucleic acid there are three primary acidic groups and one secondary.² Branched chain structures such as that depicted in (II) were therefore suggested.



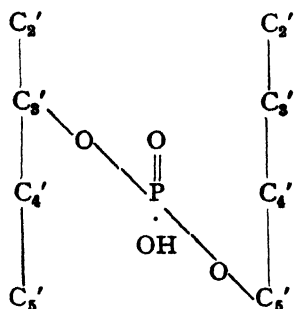
¹ E. Chargaff, *J. Biol. Chem.*, 1948, **176**, 715, 1949 **177**, 405
Gulland and D. O. Jordan, *J.*, 1944, 33.

² W. E. Fletcher, J. M.

Such structures must be regarded only as approximately correct and will doubtless be modified as the result of future research.

The deoxyribosenucleic acids may have a linear formula such as that given in (I). This is harmony with their properties including the fact that for every four phosphorus atoms there are four acidic groups.¹

In structures such as those discussed above the polynucleotides are composed of nucleotides linked together by pentose-phosphate bonds. There is considerable evidence for this. Since alkaline hydrolysis of yeast nucleic acid affords nucleotides with accompanying neutralisation of the alkali it is clear that the phosphoric acid groups participate in joining the nucleotides together. Further, since nucleic acid may be deaminated by nitrous acid without any decrease in the molecular weight, the amino groups do not take part in the internucleotide linkages. The same applies to the hydroxyl groups of guanine and uracil since they are unsubstituted in the nucleic acid molecule. This leaves only the hydroxyl groups of the pentose available. An examination of the whole question has led to the conclusion that the nucleotides are linked together in the nucleic acid molecule as follows :



The nucleotides are thus linked together through C_3' and C_5' atoms by means of phosphoric acid residues.² On this basis a plausible explanation can be given of the formation of nucleoside 2'- and 3'-phosphates when the nucleic acids are hydrolysed by alkali.

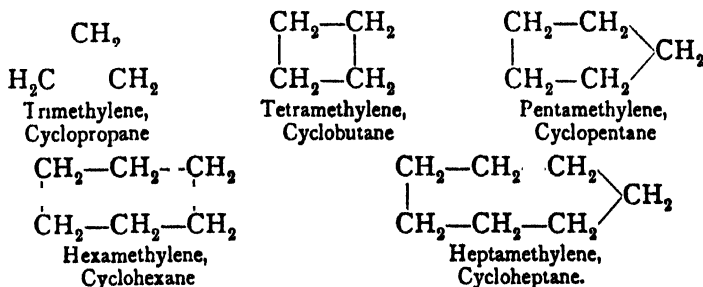
¹ D. J. Cosgrave and D. O. Jordan, *J.*, 1949, 1413.
1952, 52.

² D. M. Brown and A. R. Todd, *J.*

Chemistry of the Carbocyclic Compounds

As already stated on p. 9, compounds containing open chains are classed as aliphatic, and those containing closed chains or rings as cyclic. The following section deals with those cyclic compounds in which the rings are built up entirely of carbon atoms, and which are therefore most conveniently grouped under the heading *carbocyclic*.¹

Included in this group are certain hydrocarbons having the same composition, C_nH_{2n} , as the homologues of ethylene, although possessing very different properties. These hydrocarbons are termed poly-methylenes, or, according to the Geneva nomenclature, are named by prefixing *cyclo* to the names of the corresponding normal paraffins :



Some of these compounds give rise to large numbers of derivatives.

Of far greater interest than these hydrocarbons and their derivatives, which are often described as *alicyclic* compounds, is the large and important class made up of the true *aromatic* compounds related to benzene, C_6H_6 . Before discussing the latter in detail a brief survey of the other groups will be given.

I

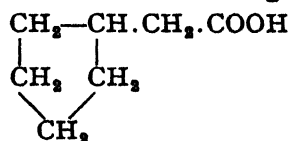
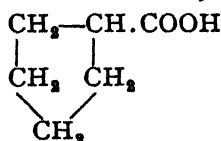
Alicyclic Compounds. Cycloparaffins

Some of the more important cycloparaffins and their physical constants are listed in the table (p. 381). It may be noted that the energy contents indicated by the last column are in agreement with Baeyer's strain theory as modified by the work of Ruzicka (see p. 382), rings larger than cyclobutane being apparently without strain.

Alicyclic compounds occur widely in nature, the majority of them containing 5- or 6-membered rings. Examples of this type are the naphthenes present in petroleum, which are hydrocarbons of the cyclopentane and cyclohexane series; the naphthenes and naphthenic acids, also

¹ These are sometimes called homocyclic or isocyclic compounds.

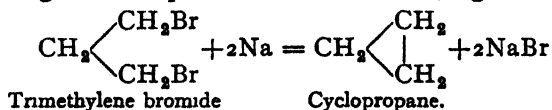
found in petroleum ; and the essential oils or terpenes, which are treated later (p. 391) on account of their interesting properties. The **naphthenes** are present in considerable quantities in Caucasian petroleum and consist mainly of cyclopentanes and cyclohexanes, together with a small percentage—about 1 per cent.—of **naphthenic acids**. These are cyclopentane monocarboxylic acids and include the following types :



The naphthenic acids are valuable chemicals, and are used in paints, inks, timber preservatives, etc.

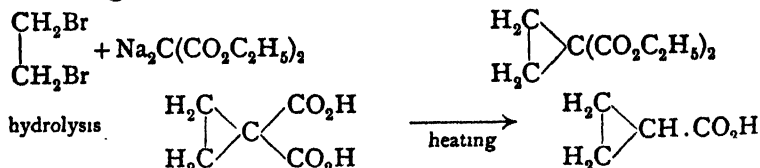
Preparation.—Compounds of this group may be synthesised by a great variety of reactions, only the more important of which can be dealt with here.

(1) Hydrocarbons can be prepared by the Wurtz reaction, by treating the corresponding dibromoparaffins with sodium, *e.g.*



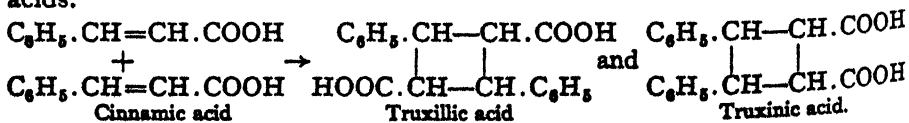
This method gives very good yields of cyclopropane derivatives, but with higher homologues various side-reactions occur.

(2) By Perkin's method from sodio-malonic ester and ethylene bromide, trimethylene bromide or tetramethylene bromide. The elimination of halogen takes place in two stages and not in the abbreviated form shown in the following scheme.



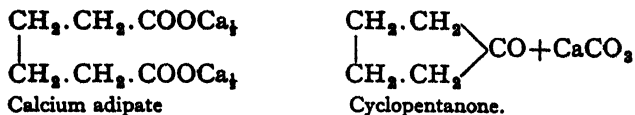
Subsequent hydrolysis of the resulting diester and heating of the dicarboxylic acid yields a mono-carboxylic derivative. The final yields agree closely with the expectation based on Baeyer's strain theory, the highest being in the cyclopentane group and the lowest in the cyclopropane group.

(3) By the condensation of unsaturated compounds. Thus cinnamic acid under the influence of light slowly polymerises to truxillic and truxinic acids.



Both of these cyclic acids occur naturally in coca-leaf (see cocaine).

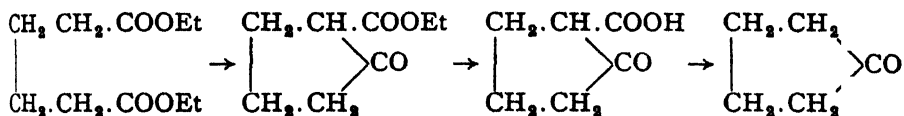
(4) Cyclic ketones are formed by the dry distillation of calcium salts of certain higher dicarboxylic acids of the oxalic acid series.



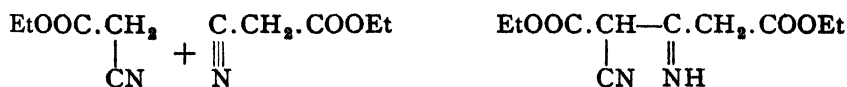
No 3-membered and few 4-membered rings can be synthesised by this method. Ruzicka has shown that with pimelic and higher acids greatly increased yields of cyclic ketones are obtained by use of the thorium salts.

A modification of the above reaction due to Blanc is to submit the anhydride of the acid to slow distillation (compare structure of the bile acids, p. 628). In this case the contraction of the ring by loss of carbon dioxide is greatly facilitated by the presence of alkyl substituents in the α or β positions to the carboxyl group.

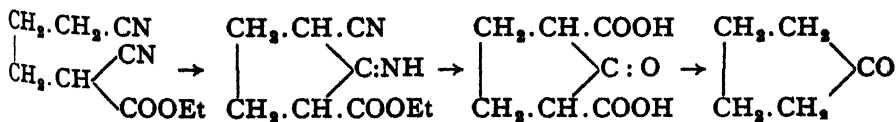
(5) By Dieckmann's method in which an appropriate dicarboxylic ester is treated with sodium to undergo an intramolecular acetoacetic ester condensation, *e.g.* with adipic ester,



(6) By *Thorpe's reaction* in which nitriles undergo condensation in the presence of sodium ethoxide to yield cyclic ketones. The mechanism of this reaction may be illustrated by the case of cyanacetic ester, two molecules of which react as follows :



With $\alpha\delta$ -dicyanovaleic ester this reaction leads to the formation of cyclopentanone dicarboxylic acid, from which cyclopentanone is obtained by loss of carbon dioxide.



This process has been adapted with great success to the synthesis of large ring compounds¹ by condensing alkylene dicyanides, $\text{NC} \cdot \text{CH}_2 \cdot (\text{CH}_2)_n \cdot \text{CH}_2 \cdot \text{CN}$, in the presence of lithium amides, LiNR_2 . These reactions must be carried out using the cyanides in high dilution in order

¹ Ziegler, Eberle and Ohlinger, *Ann.*, 1933, 504, 94.

that intramolecular and not intermolecular condensation shall predominate. Yields of the order of 40 per cent. have been obtained.

General Properties.—The cycloparaffins contain two hydrogen atoms less than the corresponding open-chain hydrocarbons, and in consequence the same number of hydrogen atoms as the corresponding open-chain olefins. Thus *n*-hexane has formula C_6H_{14} , whereas cyclohexane and *n*-hexene have the formula C_6H_{12} . Since the cycloparaffins are saturated substances with no double or triple bonds in the molecule it follows that they must have a cyclic structure if the valency rules are to hold. This ring structure has been fully established both by physical and chemical methods.

The 3-, 4-, and 5-membered rings are planar, but the six-membered rings such as cyclohexane are puckered. The important consequences of this lack of planarity of cyclohexane are discussed later. Inspection of these ring-structures shows that the cycloparaffins can furnish derivatives which exhibit both geometrical and optical isomerism (p. 45). Cyclopropane, for example, can give two dicarboxylic acids: a *cis*-acid (I) in which both carboxyl groups are above the plane of the ring, and (2) a *trans*-acid (II) in which one carboxyl group is above and the other below the plane of the ring. The *cis*-acid is symmetrical since it has a plane



of symmetry perpendicular to the plane of the ring and passing through the CH_2 group. In consequence it cannot be resolved into optical isomerides. The *trans*-acid lacks any such plane of symmetry and can be resolved into optical isomerides.

The cycloparaffins and their derivatives undergo a variety of molecular rearrangements and ring-contractions and expansions. A number of these are discussed in the chapter on the terpenes.

On examining the physical properties of the saturated compounds containing closed chains it is seen that these possess higher boiling-points and higher specific gravities than the isomeric unsaturated aliphatic hydrocarbons, and also than the saturated aliphatic compounds containing an additional two atoms of hydrogen. This may be illustrated by the following figures: cyclohexane, C_6H_{12} , b.p. 81° ; *n*-hexane, C_6H_{14} , b.p. 69° ; *n*-hexene, C_6H_{12} , b.p. 68° .

A striking feature which emerges from a closer examination of the cycloparaffins is the variation of the stability with the size of the ring.

This is evident if the heat of combustion per CH_2 group is calculated for each member of the series (see table).

	Formula.	B.p.	M.p.	d_4^{20}	Heat of Combustion in Cal. per CH_2 .
Cyclopropane . .	C_3H_6	-35°	-127°	—	168.5
Cyclobutane . .	C_4H_8	$+12^\circ$...	0.7038	165.5
Cyclopentane . .	C_5H_{10}	49°	...	0.7635	159
Cyclohexane . .	C_6H_{12}	81°	$+7^\circ$	0.7934	158
Cycloheptane . .	C_7H_{14}	117°	-12°	0.8252	158
Cyclooctane . .	C_8H_{16}	148°	$+11.5^\circ$	0.850	...
Cyclononane . .	C_9H_{18}	172°	...	0.785	...
Cyclodecane . .	$\text{C}_{10}\text{H}_{20}$	201°	$+9.6^\circ$...	158.6

Obviously cyclopropane and cyclobutane are less stable than cyclopentane and cyclohexane. Baeyer explained this in his strain theory as follows :

According to the fundamental hypothesis of stereochemistry, the four valencies of a carbon atom act in the direction of lines which may be imagined to be drawn from the central point of a tetrahedron to its summits, and thus make an angle of $109^\circ 28'$ with each other. If, however, carbon atoms unite together to form a closed chain these bonds become diverted from their natural directions, and a strain is set up which may be measured by the angle of displacement. As may easily be seen, this tension is least in the five-membered rings. Rings possessing a smaller or greater number of carbon atoms than the pentamethylene ring are under greater tension than the latter. The magnitude of the tension in any individual case is readily calculated. In the trimethylene ring, for example, the carbon atoms may be imagined to be at the corners of an equilateral triangle. The bonds joining them thus enclose angles of 60° , and the distortion of each bond is therefore $\frac{1}{2} (109^\circ 28' - 60^\circ) = 24^\circ 44'$. The following summary gives the values for the distortion in the formation of different polymethylene rings :

(Double bond)	Tri-	Tetra-	Penta-	Hexa-	Hepta-
$+54^\circ 44'$	$+24^\circ 44'$	$+9^\circ 34'$	$+0^\circ 44'$	$-5^\circ 16'$	$-9^\circ 33'$

From these figures it follows that the cyclopentane ring is under the least strain and should therefore be the most stable. In the remaining systems, on the other hand, the valency bonds tend in varying degree to assume their original positions in space and therefore to open up the ring. In the case of the above rings these theoretical deductions have been largely confirmed by experiment. In ethylene the strain is greatest, and hence the tendency to form addition compounds, with the simultaneous opening of the ring, is at its highest. This shows itself in the extraordinary speed with which ethylene adds on chlorine, bromine or hydrobromic acid. The distortion is far less in the case of cyclopropane, and consequently the opening of the ring by addition of bromine or hydrobromic

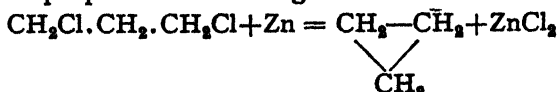
acid is effected much less readily than in the case of ethylene. Nevertheless, addition does occur, especially under the influence of light and in the presence of a peroxide.¹ The cyclobutane ring, again, is more stable than the cyclopropane ring, as is readily seen on comparing certain derivatives of these two hydrocarbons. Cyclopropane carboxylic acid, for example, is easily attacked by hydrobromic acid, whereas cyclobutane carboxylic acid under the same conditions is scarcely affected. Finally, cyclopentane and cyclohexane carboxylic acids are unchanged even on prolonged boiling with hydrobromic acid. Later work has shown that the stability of the alicyclic compounds is dependent not only on bond distortion, but also on other factors. In particular six-membered and larger rings are non-planar and strainless rings can be constructed. (This is discussed more fully on p. 384.

As has recently been shown by Ruzicka, the conditions may be quite otherwise in the case of rings containing a large number of carbon atoms. Although not readily prepared, such compounds possess a high degree of stability, and it appears that, by virtue of its magnitude, the ring is able to crumple up or twist itself into positions in which there is little or no distortion of the carbon bonds and hence no strain. Naturally occurring substances of this type are the strongly odorous ketones *muscone* and *civetone*, having 15- and 17-membered rings respectively (see p. 386).² For rings containing more than 20 carbon atoms it is probable that the arrangement in the solid is one of double parallel chains,³ the straight portions of which have a structure identical with that of the normal paraffins.

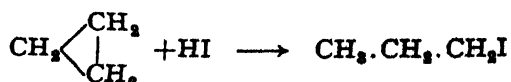
Many hydroaromatic compounds are distinguished by the ease with which they be transformed into the corresponding aromatic compounds. Examples of such **aromatisations** will be found in the sequel.

As has already been stated, the most important group of alicyclic compounds, known as the terpenes or essential oils, is dealt with later. A brief description is given here of some of the simple hydrocarbons and their derivatives.

Cyclopropane, C_3H_6 , is manufactured by chlorinating propane to give 1 : 3-dichloropropane and treating this with zinc.



It is a gas (b.p. -35°). The strain in the 3-membered ring is illustrated by the ease with which it is ruptured to form open-chain derivatives. Thus cyclopropane reacts readily with hydrogen iodide to yield iodo-propane. With bromine in sunlight it is converted comparatively rapidly

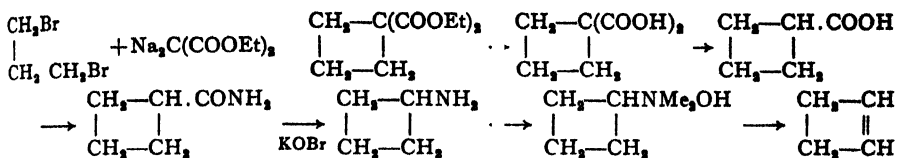


¹ Kharasch, Fineman and Mayo, *J.A.C.S.*, 1939, 61, 2139.
Acta, 1926, 9, 339. *Chem. and Ind.*, 1935, 54, 2.

² Ruzicka, *Helv. Chim.*

into 1 : 3-dibromopropane; with hydrogen and colloidal palladium in acetic acid solution propane is formed. Under the influence of heat, especially in the presence of a catalyst such as iron filings or platinum, the ring is opened with the formation of propylene, $\text{CH}_3\cdot\text{CH}:\text{CH}_2$. On the other hand, cyclopropane is not attacked by cold potassium permanganate solution, or by ozone. It is now used extensively as an anæsthetic.

Cyclobutane, C_4H_8 , is a liquid boiling at $+12^\circ$. It was prepared by Willstätter through the intermediate compound *cyclobutene*, which was obtained by distilling the quaternary ammonium hydroxide of aminocyclobutane. Starting from trimethylene bromide and sodiummalonic ester, the process involved the following steps :



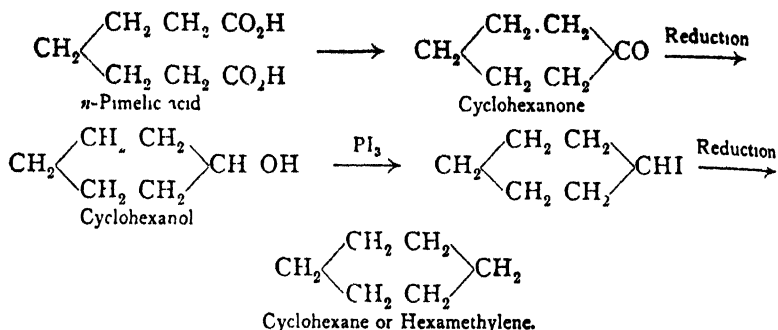
On reducing cyclobutene catalytically with hydrogen and nickel at 100° pure cyclobutane was obtained. If the reduction is carried out at the more usual temperature of $180\text{--}200^\circ$, the ring is ruptured and the product is butane. Cyclobutane is not attacked by hydriodic acid or by permanganate in the cold.

Cyclopentane, C_5H_{10} , b.p. 49° , may be prepared from 1 : 5-dibromopentane and zinc, or by reduction of the easily accessible *cyclopentanone*. It occurs naturally in the naphthenes present in Caucasian and American petroleum.

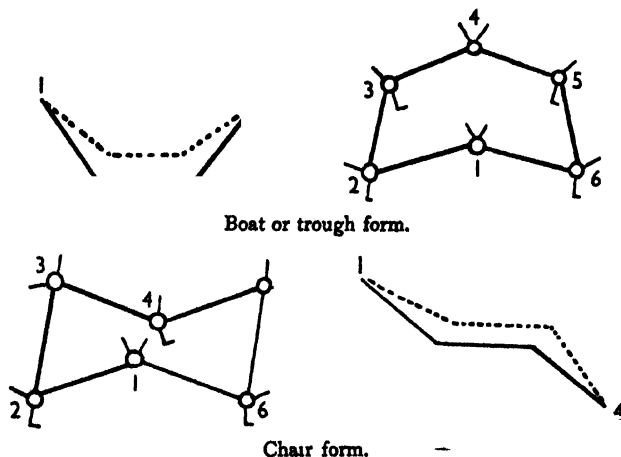
Cyclopentane is unaffected by bromine in the dark, but in light it undergoes normal substitution to form *bromocyclopentane*. The latter is converted into the unsaturated compound cyclopentene on treatment with alcoholic potash. The cyclopentane ring is not opened by catalytic hydrogenation with nickel below 300° .

Zelinsky observed that when 1-methyl-3-cyclopentanone is led over nickel at 250° it yields methyl-cyclopentane, b.p. 72° . This is a convenient method of preparing the compound. No rupture of the ring occurs in this reaction, despite the comparatively high temperature and presence of nickel catalyst.

Cyclohexane, *hexa-hydrobenzene*, C_6H_{12} , is manufactured from pure benzene by catalytic reduction. Its structure is thus established, and has been confirmed by synthesis. Cyclic ketones, as already explained, are produced by distilling the calcium salts of dibasic acids, cyclohexanone, for example, being obtained from calcium pimelate. Cyclohexane itself was first synthesised by Baeyer in the following stages : Cyclohexane is an important constituent of Caucasian petroleum and is a colourless liquid, b.p. 81° , m.p. $6\cdot4^\circ$, with a smell like benzene. It is easily oxidised to adipic acid by nitric acid.



Stereochemistry of cyclohexane derivatives.¹ A theory of strainless rings, *i.e.* rings in which the valency angles of the ring carbon bonds are $109^\circ 28'$, was put forward as early as 1890 in a mathematical paper by Sachse and was revived in a more definite form in 1918 by Mohr. It is assumed that while rings with 3, 4, or 5 carbon atoms have a planar or nearly planar structure the cyclohexane ring may become completely strainless by assuming a puckered or folded form. Two models are possible on the basis of the tetrahedral carbon atom and are represented below:² the non-rigid *boat* or *trough* conformation and the semi-rigid

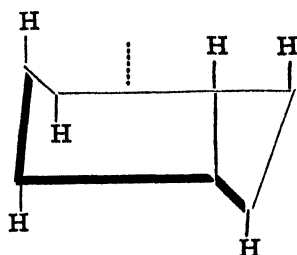


chair conformation. The word conformation denotes these arrangements in space of the atoms in a molecule which are free from strain and which are not superposable.³ Ethane, for example, may adopt an infinite number of conformations merely by rotation of the methyl groups round the carbon-carbon linkage. It is characteristic that when a molecule changes from one conformation to another no bond is broken and no new linkage is formed.

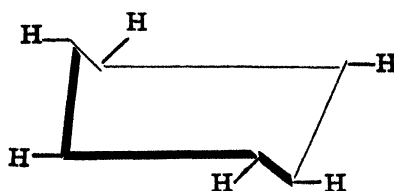
¹ O. Hassel, *Research*, 1950, 3, 504. *Quart. Reviews*, 1953, 7, 221. A. J. Birch, *Ann. Reports*, 1951, 48, 192. D. H. R. Barton, *J.*, 1953, 1027. ² In these diagrams the models may be pictured as being supported on a table by the bonds drawn as a letter L. ³ W. N. Haworth *The Constitution of Sugars*, p. 90

In recent years investigations by physical and chemical methods have given a deeper insight into the stability of the cyclohexane conformations. This is largely based on the work of O. Hassel. The energy barrier between the chair and boat forms is not great, but is sufficient to make the chair form greatly predominate at ordinary temperatures. In fact, except in certain compounds with bridged structures, cyclohexane and other similar six-membered ring compounds are obtained only in the chair form.

Examination of the chair form of cyclohexane shows that the carbon-hydrogen bonds can be divided into two geometrically different types (see I and II, in which for the sake of clarity the two types of bonds are shown in separate diagrams).



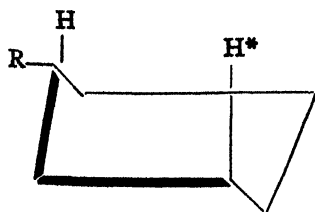
(I)



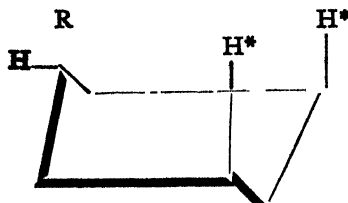
(II)

The C—H bonds of the first group are parallel to the symmetry axis of the molecule. These vertical bonds are known as *polar* or *axial bonds* (I). The remaining six C—H bonds project from the ring and are termed *equatorial bonds* (II).

This model has given rise to a number of interesting and important consequences. Hassel showed that in a substituted cyclohexane the conformation adopted is that with the maximum number of equatorial substituents. This is undoubtedly due to equatorial substituents being less subject to interaction with hydrogen or other atoms in the molecule. For example, in a monosubstituted cyclohexane the substituent can be either equatorial (III) or axial (IV). In the second case the substituent interferes sterically with the C_3 - and C_5 -hydrogen atoms (H^*), and



(III)

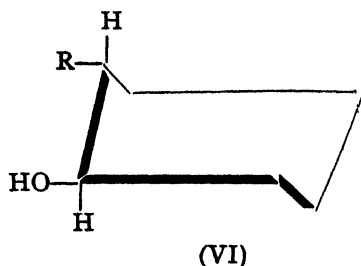
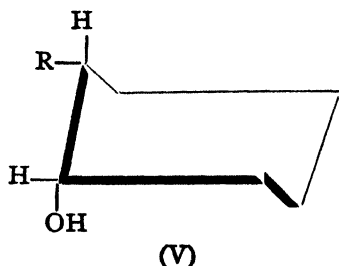


(IV)

consequently the equatorial position is occupied. In other words, at a given carbon atom in a cyclohexane ring, an equatorial substituent gives rise to a more stable product than an axial substituent.

Certain reactions can be used to assign conformations to cyclohexane derivatives. The formation of olefinic compounds by the acid-catalysed dehydration of hydroxy-compounds occurs more readily when the reaction

fragment $\begin{array}{c} | & | \\ \text{H}-\text{C}-\text{C}-\text{OH} \\ | & | \end{array}$ lies in a plane. It follows that the cyclohexanol (V) in which the OH group and the adjacent H atom are both axial is dehydrated more readily than when one is axial and the other equatorial (VI).



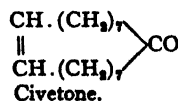
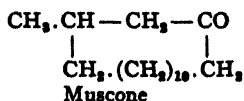
The stereochemistry of condensed ring systems is discussed later on p. 587.

Cyclo-octanone is an example of a cyclo-octane derivative. It is formed in small amounts (5 per cent.) when the calcium salt of azelaic acid is distilled. According to Ruzicka, yields of 25 per cent. may be obtained by distilling the thorium salt.

Cyclo-nonanone is obtained in small yield by the dry distillation of thorium sebacate. It boils at 95° to 97° under a pressure of 17 to 18 mm. When reduced in boiling alcoholic solution with metallic sodium it yields cyclo-nonane. (See table on p. 381.)

Monocyclic ketones containing 16, 18 and 30 carbon atoms respectively in the ring have also been synthesised, and Ziegler has obtained a triketone with 45 carbon atoms.

Naturally occurring compounds of this type are the powerfully odorous ketones **muscone** (from the musk deer) and **civetone** (from the civet cat). **Muscone**, $\text{C}_{15}\text{H}_{26}\text{O}$,



is a saturated optically active liquid, which has been shown by Ruzicka to contain a 15-membered ring. **Civetone**, $\text{C}_{17}\text{H}_{30}\text{O}$, melts at 31°. It is a symmetrical unsaturated ketone which yields azelaic acid on oxidation.

Derivatives of Cyclohexane

Benzene hexachloride, $\text{C}_6\text{H}_6\text{Cl}_6$, is prepared by the action of chlorine on benzene in the presence of light. Theoretically it can exist in several stereoisomeric forms (*cf.* inositol), five of which have been isolated from the product of the above reaction¹: α , m.p. 158°; β , m.p. 309°; γ , m.p. 112°; δ , m.p. 138-139°; ϵ , m.p. 219°. They are colourless crystalline compounds. Benzene hexachloride is a valuable insecticide (*Gammexane*), its toxicity being due almost entirely to the γ -compound¹

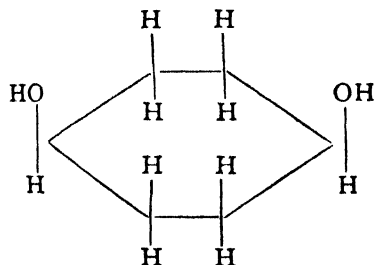
¹ R. E. Slade, *Chemical Age*, 1945, 52, 244. K. C. Kauer, R. B. DuVall and F. N. Alquist, *Ind. Eng. Chem.*, 1947, 39, 1335.

It ranks high among the other insecticides at present in common use—pyrethrum, derris, nicotine, hydrocyanic acid, *p*-dichlorobenzene, D.D.T., and the organic isocyanates.

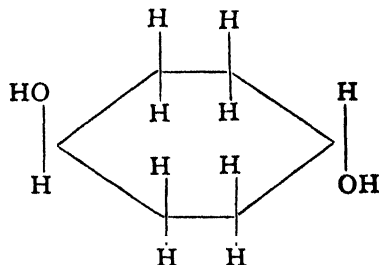
Cyclohexanol, *hexahydrophenol*, $C_6H_{11}.OH$, is produced in good yield by leading a mixture of phenol vapour and hydrogen over finely-divided nickel at 140° to 160° . It is a colourless liquid, b.p. 160.5° , which solidifies at a low temperature to a mass of melting-point 20° . With hydrobromic acid it yields *monobromocyclohexane*, b.p. 162° . When hexahydrophenol is heated with oxalic acid, water is eliminated and tetrahydrobenzene formed. Cyclohexanol is oxidised catalytically or by nitric acid to adipic acid and is therefore an important intermediate in the manufacture of nylon.

Quinitol, *cyclohexane-1:4-diol*, (hexahydro - hydroquinone), was obtained by Baeyer, by reducing cyclohexane-1:4-dione with sodium amalgam. It exists in two stereoisomeric forms.

This type of isomerism is similar to that described under fumaric and maleic acids (p. 289), the ring structure hindering free rotation of the carbon atoms in the same manner as the double bond of the ethylene



cis-Quinitol, m.p. 102°



trans-Quinitol, m.p. 139° .

series. Theory therefore predicts that each disubstitution product of a polymethylene should exist in two stereoisomeric forms, according as the substituent atoms or groups lie on the same or on opposite sides of the plane of the ring. In agreement with this, two isomeric quinitols are known, corresponding to the above formulæ. These differ in their configuration in such a way that in *cis*-quinitol the hydroxyl groups lie on the same side, and in *trans*-quinitol on opposite sides of the plane of the ring.

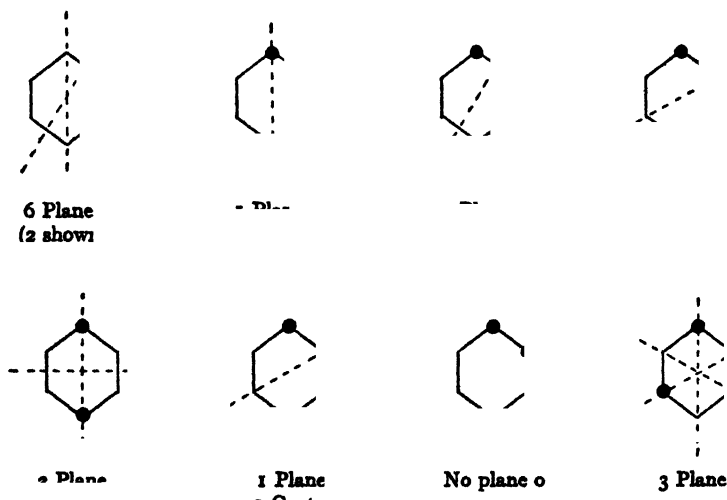
Quercitol, *cyclohexane-pentol*, $C_6H_7(OH)_5$, is found in an optically active form in acorns (hence *acorn sugar*). It melts at 235° .

Inositols, $C_6H_8(OH)_6$, are hexahydroxy-*cyclohexanes*. They are soluble in water and have a sweet taste. One of them, *meso*-inositol,¹ (*myoinositol*) m.p. 225° , is a component of "bios," the growth-stimulating factor for yeast. Other bios components are pantothenic acid, biotin, and aneurin. Inositol is therefore frequently included in the vitamins of the B group.

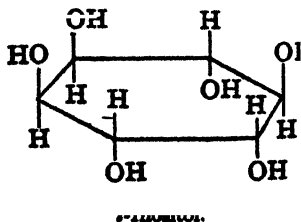
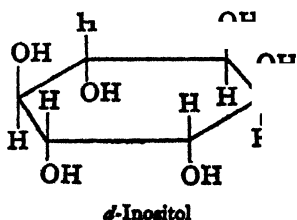
¹ For a review of T. Posternak's work on the configuration of mesoinositol see J. K. N. Jones, *Annual Reports*, 1946, 43, 167.

The inositols are of interest as providing the first known optical active compounds containing no asymmetric carbon atom (see below pp. 38, 547.)

In the inositol molecule the hydrogen atoms and hydroxyl groups lie above and below the plane of the ring and as a result there are theoretically eight geometrical isomers as shown by the formulæ given below. In these formulæ the plane of the ring is supposed to lie in the plane of the paper and the hydroxyl groups lying above this plane are indicated by heavy marks: planes and centres of symmetry are also given.



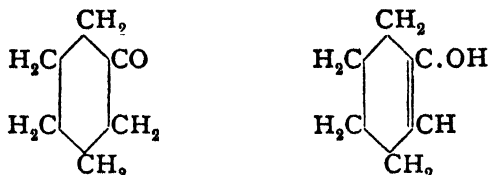
Only one form is without a plane or centre of symmetry and therefore gives rise to two enantiomorphs as shown.



Cyclohexanone is formed by heating the calcium salt of *n*-pimelic acid (see p. 288), and can be prepared by oxidation of the corresponding alcohol cyclohexanol. It is manufactured by passing the vapour of cyclohexanol over a heated copper catalyst. It is an oil, b.p. 155° , with a smell of peppermint and on reduction yields cyclohexanol.

Cyclohexanone is a tautomeric compound and may react either as a ketone or as a hydrogenated phenol (Δ^1 -tetrahydro-phenol).

As a ketone it unites with hydroxylamine and sodium bisulphite, and as a phenol it may be acetylated by boiling with acetic anhydride to form the acetyl ester of Δ^1 -tetrahydro-phenol, b.p. 180° to 181° .

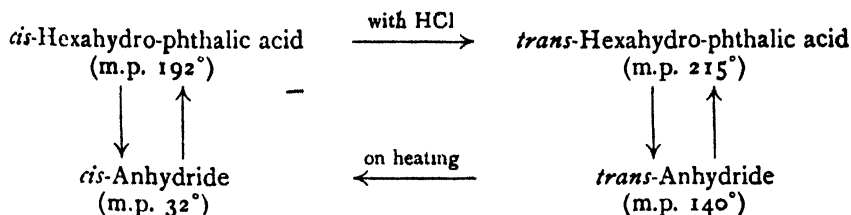


Hydro-aromatic carboxylic acids resemble aliphatic acids in their properties. The following compounds of this type may be mentioned.

Quinic acid, *tetrahydroxy-hexahydro-benzoic acid*, $(\text{HO})_4\text{C}_6\text{H}_7\text{COOH}$, is present in cinchona bark, coffee beans, sugar beet and other sources. The acid prepared from cinchona bark is optically active and melts at 162° . It is also known in an inactive form. On oxidation it is converted into quinone, and when heated with hydriodic acid gives benzoic acid.

The **hydro-phthalic acids** were carefully examined by Baeyer in an attempt to determine the constitution of benzene. Although unsuccessful in this respect, these arduous investigations brought to light the existence of a number of isomerides, since both structural isomerism and stereo-isomerism may occur among these compounds.

Thus the reduction of phthalic acid has led to the isolation of eleven different *dihydro-phthalic acids*, $\text{C}_6\text{H}_8(\text{COOH})_2$, four *tetrahydro-phthalic acids*, $\text{C}_6\text{H}_8(\text{COOH})_2$, and two *hexahydro-phthalic acids*, $\text{C}_6\text{H}_{10}(\text{COOH})_2$. Several hydro-derivatives of terephthalic and isophthalic acids are also known. We are dealing here with the same type of geometrical isomerism as was outlined in connection with quinitol (p. 387), i.e. *cis-trans* isomerism. In their interconversions the isomerides recall the behaviour of ethylene derivatives, as is seen in the case of the hexahydro-phthalic acids.



UNSATURATED ALICYCLIC COMPOUNDS¹

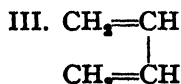
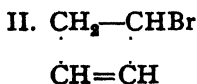
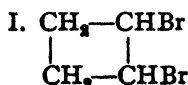
The most important cyclo-olefins from the theoretical point of view are those containing conjugated double bonds. Benzene, for example, which is most simply formulated as cyclohexatriene (p. 431), is "aromatic" in its properties and behaves as a polyolefinic compound only to a very

¹ See also Wilson Baker, "Non-benzenoid Aromatic Hydrocarbons," *J.*, 1945, 258.

limited extent. This unique behaviour has been the subject of great controversy and speculation, and it is obviously relevant to study the properties of other ring systems with conjugated double bonds. It may be said at once that, as shown later, the properties of benzene are not peculiar to the six-membered ring, C_6H_6 , since other conjugated cyclo-olefins have been prepared which behave as truly aromatic substances.

The unsaturated alicyclic compounds (or **cyclo-olefins**) bear the same relationship to the cycloparaffins as the olefins to the paraffins. They can be prepared by similar methods such as dehydration of the corresponding alcohols, or dehalogenation of the halides, etc. The less stable members such as cyclopropene and cyclobutene require milder reactions. Cyclobutene, for instance, is obtained by the thermal decomposition of cyclobutyltrimethylammonium hydroxide.

The simplest cycloalkadiene, cyclobutadiene, has never been isolated. All attempts to remove hydrogen bromide from 1 : 2-dibromocyclobutane (I) by potassium hydroxide have led either to the formation of bromo-

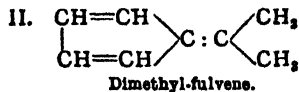
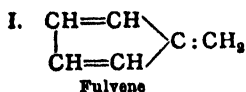


cyclobutene (II) or acetylene. Treatment with quinoline converts the dibromocyclobutane into butadiene (III) and other products. It may be here noted that a derivative of cyclobutadiene, diphenylene, has been prepared (p. 616).

Cyclopentadiene, $\begin{array}{c} \text{CH}=\text{CH} \\ | \\ \text{CH}=\text{CH} \end{array} \text{CH}_2$, is a colourless liquid, b.p. 41° , which is obtained

in the first runnings of the crude benzene from coal tar. It readily polymerises, and at temperatures up to 100° yields chiefly dicyclopentadiene, $C_{10}H_{12}$. Above this, *eg* at 135° , polycyclopentadienes $(C_5H_6)_n$ are also formed.

In cyclopentadiene the two hydrogen atoms of the CH_2 group are very reactive, owing to the proximity of the two double bonds; one of them, for example, may be replaced by potassium. Further, under the influence of sodium hydroxide or ethoxide, cyclopentadiene condenses with aldehydes and ketones, the CH_2 group of the former reacting with the $\text{C}:\text{O}$ group of the latter with elimination of water. The resulting condensation products, of which that with acetone possesses the structure II, have an intense orange to blood-red colour, and may be represented as substitution products of an isomeride of benzene having the formula I. Thiele calls this unknown hydrocarbon fulvene.



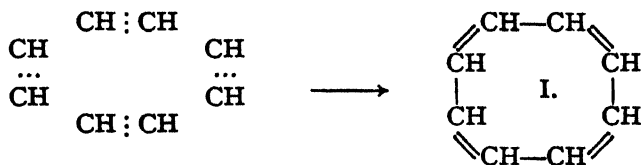
The fulvenes provide an interesting illustration of the manner in which the colour of an organic compound is influenced by the presence and arrangement of double bonds within the molecule.

Cycloheptatriene, tropilidene, $\begin{array}{c} \text{CH}.\text{CH}:\text{CH} \\ || \\ \text{CH}.\text{CH}:\text{CH} \end{array} \text{CH}_2$, is a degradation

product of the alkaloids cocaine and atropine, and can be prepared

from suberone. It is a liquid, b.p. 116° , which smells of leeks. The alkaloid colchicine is a derivative of cyclo-heptatriene and contains the 3 : 4 : 5 : 6-dibenzcyclo-hepta-1 : 3 : 5-triene system. This readily yields phenanthrene derivatives on oxidation and isomerises to 9-methylphenanthrene,¹ the seven-membered ring giving rise to the more stable benzenoid structure.

Cyclooctatetraene (I) is of particular interest because it is an analogue of benzene. It was first obtained by the exhaustive methylation of pseudo-pelletierine, an alkaloid found in the pomegranate.² It is now prepared by the polymerisation of acetylene under pressure in tetrahydrofuran in presence of nickel cyanide or halogenide.³



It is a golden-yellow liquid with pronounced unsaturated properties. It is reduced catalytically until four molecules of hydrogen are absorbed and cyclooctane obtained. It also reacts with bromine, chlorine, maleic anhydride, etc. It is obvious, therefore, that cyclooctatetraene is a highly unsaturated substance, quite different from benzene. This fundamental difference between the two compounds is probably due, at least in part, to the non-planar structure of cyclooctatetraene.

Evidence including infra-red and Raman spectra measurements leaves no doubt that cyclooctatetraene has a puckered ring.⁴

Cyclooctatetraene undergoes a number of most interesting reactions to yield phenylacetaldehyde, terephthaldehyde, etc.⁵

Cyclooctatetraene with certain reagents undergoes *ring-contraction* with formation of aromatic compounds. With hypochlorous acid in alkaline solution, for example, terephthaldehyde is obtained.

TERPENES AND CAMPHORS⁶

Essential oils are pleasant-smelling substances obtained by the steam-distillation or extraction of the leaves, flowers, etc., of plants and trees. Many of them are complex mixtures, though some, such as oil of bitter almond (benzaldehyde) and oil of wintergreen (methyl salicylate), consist mainly of one constituent. Among the chief constituents are the

¹ J. W. Cook, G. T. Dickson and J. D. Loudon, *J.*, 1947, 746. ² Willstätter and Waser, *Ber.*, 1911, 44, 3423. Willstätter and Heidelberger, *Ber.*, 1913, 46, 517. Cf. A. C. Cope, *J.A.C.S.*, 1947, 69, 976. ³ W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Ann.*, 1948, 560, 1.

⁴ W. B. Person, G. C. Pimentel and K. S. Pitzer, *J.A.C.S.*, 1952, 74, 3437. ⁵ Reppe *et al.*, *loc. cit.*; N. Campbell, *Ann. Reports*, 1947, 54, 120. ⁶ *The Terpenes*, J. L. Simonsen and L. N. Owen (Cambridge University Press, 1947). *Natural Terpenes*, J. W. Baker (Methuen, 1930). *Some Aspects of Terpene Chemistry*, L. N. Owen and J. L. Simonsen, *Endeavour*, 1949, 8, 26. R. P. Linstead, *Ann. Reports*, 1935, 32, 316. F. B. Kipping, *ibid.*, 1938, 35, 268.

terpenes (cyclic hydrocarbons of the formula $(C_5H_8)_n$) and their oxygen derivatives, alcohols and ketones, which are classed under the name of **camphors**, as well as certain closely related open-chain alcohols, aldehydes and ketones, related to the open-chain aliphatic terpenes. Terpenes and essential oils were the subject of many careful investigations by Otto Wallach, von Baeyer, Semmler, Tiemann, W. H. Perkin, Jr., and a host of others, and in recent times by G. Komppa, J. Read, L. Ruzicka, J. L. Simonsen, etc.

Strictly speaking, the term "terpene" is applied to cyclic hydrocarbons of the formula $C_{10}H_{16}$, but it now has a wider meaning and includes :

- | | |
|----------------------------------|-----------------------------------|
| 1. Hemi-terpenes, C_5H_8 | 3. Sesquiterpenes, $C_{15}H_{24}$ |
| 2. True Terpenes, $C_{10}H_{16}$ | 4. Polyterpenes |
| (a) Open-chain | (a) Diterpenes, $C_{20}H_{32}$ |
| (b) Monocyclic | (b) Triterpenes, $C_{30}H_{48}$ |
| (c) Dicyclic | |

General Properties and Chemical Behaviour.—With few exceptions the terpenes are colourless, strongly-refracting liquids, insoluble in water and readily volatile in steam. They are characterised by a pleasant smell, and many of them are optically active.

The terpenes contain one or more double bonds and consequently unite with chlorine, bromine, and hydrogen halides to form halogen-substituted compounds, which are of interest as being intermediate products in the transformation of terpenes into terpene alcohols. Characteristic addition compounds are formed by N_2O_3 , N_2O_4 , $NOCl$, and $NOBr$ to yield nitrosites, nitrosates, nitroso-chlorides, and nitrosobromides respectively (see p. 169). The introduction of nitrosyl chloride by Tilden (1877) as a reagent for identifying terpenes is reminiscent of Emil Fischer's introduction of phenylhydrazine into carbohydrate chemistry.

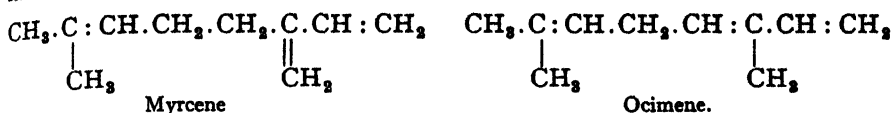
A number of the terpenes are labile, readily isomerising under the influence of acids into more stable forms.

As might be anticipated, oxidative methods play a large part in determining the structure of the terpenes. In no other field is ozone used to such an extent, while dehydrogenation to simple aromatic compounds has also been of great service. Use is also made of the Diels-Alder reaction and isomerisation to compounds of known structure. Care must be exercised in all terpene work, however, as the migration of double bonds which frequently occurs is often not readily detected.

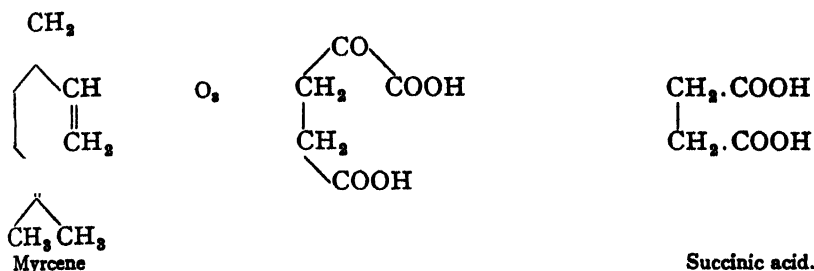
Aliphatic Terpenes

Two of the commoner open-chain terpenes are **myrcene** which occurs in bay oil, and **ocimene** from oil of *Ocimum basilicum*. Both have the formula $C_{10}H_{16}$ and differ only in the position of their double bonds. Ocimene yields 95-96 per cent. of acetone on ozonolysis and must therefore exist mainly or entirely in the *isopropylidene* form, with the $(CH_3)_2C : CH$.

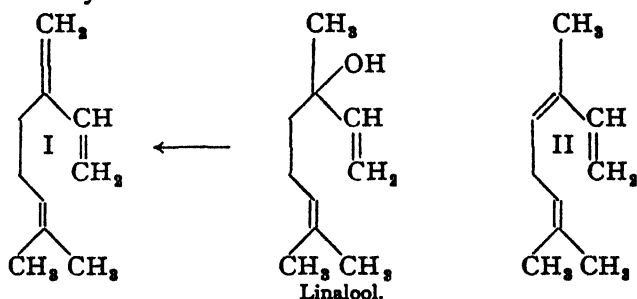
grouping¹ (*cf.*, however, p. 394). Most natural oils including myrcene, linalool, and geraniol, appear to contain only the isopropylidene forms.²



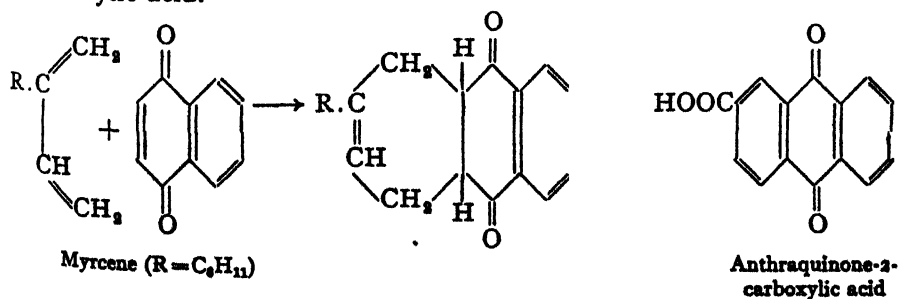
The assigned structure of myrcene agrees with the results of ozonisation experiments in which succinic acid is obtained



It is obtained by the dehydration of linalool, a process which may occur in two ways:—



That dehydration results in the formation of I (myrcene) and not II was shown by condensing the product with naphthaquinone.³ The condensation product on dehydrogenation and oxidation gave anthraquinone-2-carboxylic acid: had the product of dehydration possessed formula II, the above procedure would have yielded anthraquinone-1 : 2-dicarboxylic acid.

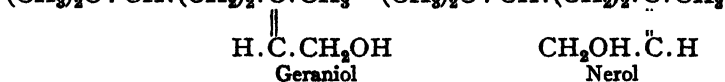


¹ M. D. Sutherland, *J.A.C.S.*, 1952, 74, 2688. ² J. Doeve, *Bull. Chim. Soc.*, 1936, 3, 613. Y. R. Neves, *ibid.*, 1951, 28, 506. ³ B. A. Arbusov and W. S. Abramson, *Ber.*, 1934, 67, 1942.

A number of unsaturated alcohols and their corresponding aldehydes are found in the essential oils associated with open-chain and cyclic terpenes, to which they are closely related in structure. They are known as *olefinic* or *open-chain terpene alcohols*. Well-known examples of this class are *geraniol*, *nerol*, *linalool* and *citronellol*.

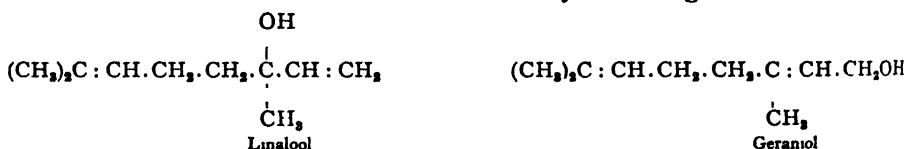
Geraniol is a pleasant-smelling liquid, b.p. $121^{\circ}/17$ mm. It may be obtained from geranium oil or by the reduction of the aldehyde citral, into which it is again transformed on oxidation. Geraniol is the chief constituent of geranium oil, rose oil, and lemon-grass oil. **Nerol**, a geometrical isomeride of geraniol, has an odour of roses and, like geraniol, is a valuable constituent of perfumes.

Both geraniol and nerol with dilute sulphuric acid are converted to

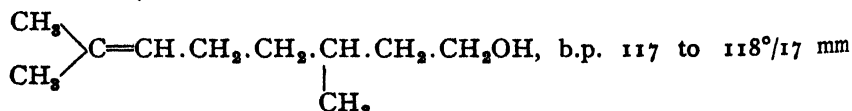


the cyclic terpenes, α -terpineol and terpin hydrate. Since nerol undergoes this conversion nine times as rapidly as geraniol it is regarded as the *cis*-compound. Geraniol consequently is the *trans*-isomer.

Linalool, an isomer of geraniol and nerol, occurs in optically active forms and has an odour similar to that of lily of the valley. It is labile and isomerises on treatment with acetic anhydride to geraniol.

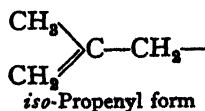
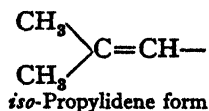


Citronellol,



occurs in the (—)-form in rose oil and in the (+)-form in citronella oil.

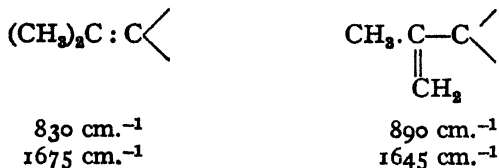
As in many other compounds of this type, the terminal group appears to react in two forms.



For example, apparently homogeneous compounds with this group on ozonisation frequently yield both acetone and formaldehyde, thus suggesting that we are dealing with mixtures of tautomeric compounds. Much of the evidence has been conflicting, but recent infra-red absorption measurements on carefully purified citronellal, citronellol, and geraniol show that these substances possess only the *isopropylidene* group, the isomeric form being present only to a slight extent.¹ This result has been

¹ H. W. Thompson *et al.*, *J.*, 1950, 3457. G. B. B. M. Sutherland *et al.*, *J.*, 1950, 915.

achieved by making use of the strong absorption bands of the *isopropylidene* and *isopropenyl* groups :



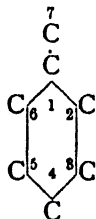
The pure terpenes mentioned above show no bands at 890 and 1645 cm^{-1} , but exhibit absorption at 830 and 1675 cm^{-1} . It must be concluded that these substances exist entirely or almost entirely in the *isopropylidene* form, and this applies to other aliphatic terpenes such as linalool and nerol. It also follows that the evidence provided by oxidative degradation is unreliable. The oxidation of nerol and geraniol yields sufficient formaldehyde to indicate that they contain about 20 per cent. of the *isopropenyl* form, whereas the infra-red evidence shows that this form cannot be present except to a slight extent.

Monocyclic Terpenes and Camphors

Nomenclature.—The majority of the monocyclic terpenes are derived from *p*-cymene, and a few from *m*-cymene. The structure of these compounds is expressed by reference to the saturated parent hydrocarbon, *e.g.* hexahydrocymene, the carbon atoms of which are numbered as in the annexed formula. The position of the double bond is indicated in the usual way (see p. 395), a double bond between the atoms 2 and 3 being shown by Δ^2 .

Hexahydrocymene, commonly known as *menthane*, is not found in nature but may be prepared by reducing *p*-cymene with hydrogen and finely divided nickel.

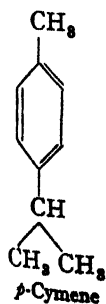
Tetrahydro-cymenes are therefore described as *menthenes*, and dihydro-cymenes as *menthadienes*.



Terpenes

The monocyclic terpenes are dihydrocymenes and may therefore be regarded as partially reduced benzene derivatives. They are pleasant-smelling liquids exhibiting the properties of unsaturated compounds. They combine with two mols. bromine, hydrochloric acid, nitrosyl chloride, etc., and are readily oxidised with ozone, etc. Most terpenes are optically active and are found in nature in both the (+)- and (–)-forms.

The ease with which they are converted into aromatic hydrocarbons is characteristic of the monocyclic terpenes, and their skeletal structure has been shown by their dehydrogenation into *p*-cymene, *p*-isopropyl-methylbenzene. The true terpenes are thus six-membered ring-compounds with methyl and *isopropyl* groups para to one another. It should be noted

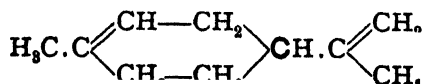


methyl and

too that these substances with formula $C_{10}H_{16}$ have been found to possess only two double bonds and therefore require a cyclic structure (*cf.* the aliphatic terpenes with three double bonds).

A number of the terpenes are labile, readily isomerising under the influence of acids.

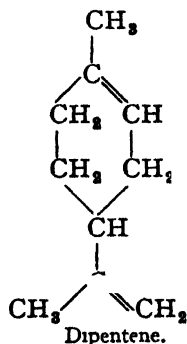
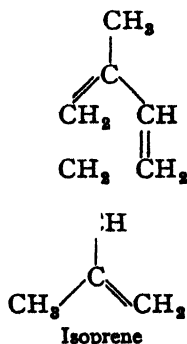
Limonene, Δ^1 -*8-menthadiene*,



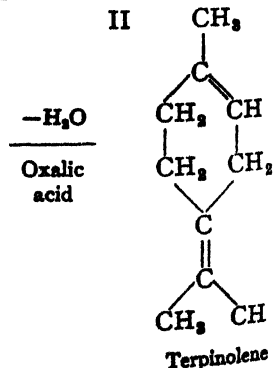
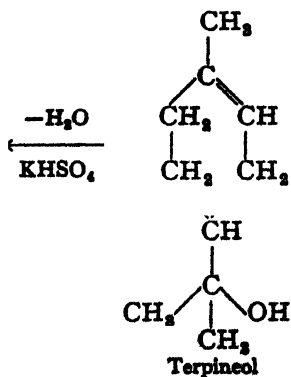
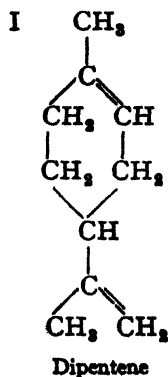
exists in dextro-, lævo-, and inactive forms.

(+)-**Limonene** is the chief constituent of the oils of lemon, bitter orange, etc.; (−)-limonene is found with (+)-pinene in pine-needle oil. Both forms are liquids of boiling-point 177° , with a strong smell of lemons.

(±)-**Limonene**, *dipentene*, is obtained by mixing equal quantities of +- and − limonenes, or (in poor yield) by the polymerisation of isoprene. In the reverse process, dipentene can be converted into isoprene in 60 per cent. yield by pyrolysis. The relationship of terpenes of different types to isoprene is stressed on p. 418.



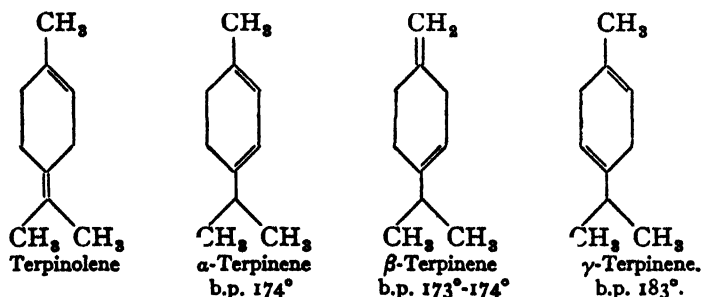
Limonene has two double bonds since it forms a dihydrochloride and a tetrabromide. It is dehydrogenated either by sulphur or through its bromine derivative to *p*-cymene. The structure has been established from its relationship to that of terpineol, Δ^1 -menthen-8-ol (p. 398) which loses water in two ways giving either limonene or terpinolene.



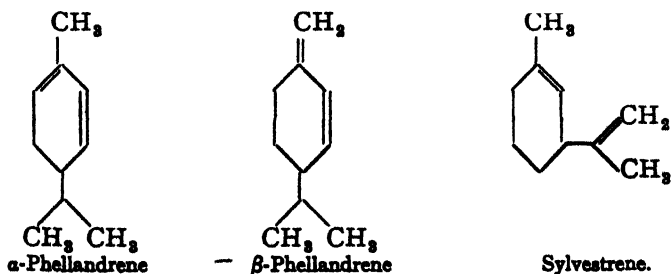
The symmetrical formula II is assigned to terpinolene which does not exist in optically active forms : formula I, on the other hand, contains the asymmetric carbon atom necessary for dipentene. It follows that the double bonds in dipentene are in the 1 : 2 and 8 : 9 positions. The accepted formula fully accounts for its chemical properties : for example, its conversion into carvone (p. 402).

Terpinolene, $\Delta^{1:4(8)}$ -*menthadiene*, is obtained as already mentioned by heating terpineol with oxalic acid solution. It boils at 183° - 185° , and on treatment with acids isomerises to "terpinene," a mixture of three isomers. It does not exist in optically active forms.

α - and γ -Terpinenes are present in cardamon oil and are optically inactive. β -Terpinene is known, but does not occur naturally.



α - and β -Phellandrenes.—The α -compound occurs both in the + and - forms in many essential oils. The β -compound occurs in oil of water fennel.



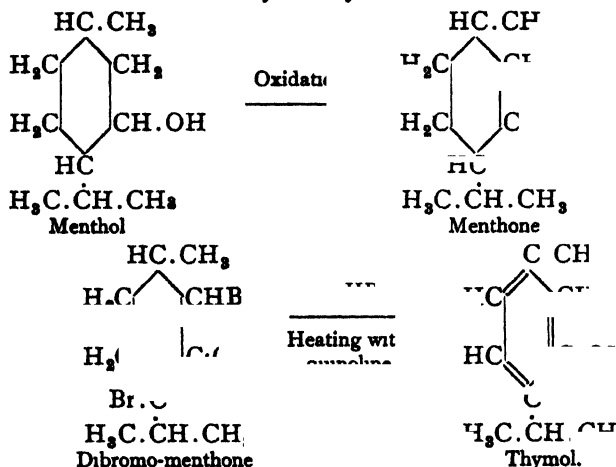
The phellandrenes readily undergo change with acids into dipentene and terpinene.

The above compounds are *p*-menthadienes. An example of a *m*-menthadiene is (+)-sylvestrene, $\Delta^{1:8(9)}$ -*m*-menthadiene, b.p. 176° ; it is the limonene of the *m*-cymene series and has been prepared from Swedish and Russian turpentine. Simonsen and Rao showed that it does not occur naturally in these sources, but is formed from the carene present by secondary changes due to the treatment of the oils with hydrogen chloride (see p. 404). The structure of sylvestrene has been shown by converting it into *m*-cymene and by synthesis.

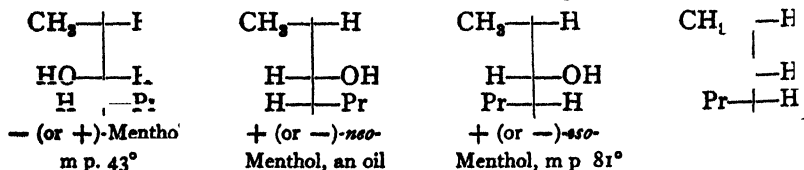
Carvestrene is (\pm)-sylvestrene.

Alcohols and Ketones

(-)-Menthol, 3-menthanol, is the odorous, chief constituent of oil of peppermint, from which it may be separated in the solid state. It melts at 143° , boils at 216° , and is employed as an antiseptic and anæsthetic. As a secondary alcohol menthol is oxidised by potassium dichromate to the ketone, menthone, b.p. 207° , which also occurs in oil of peppermint and has a peppermint odour. The structure of menthol has been elucidated by reduction (hydriodic acid) to hexahydro-*p*-cymene and the dehydrogenation of menthone to thymol by means of bromine and quinoline.



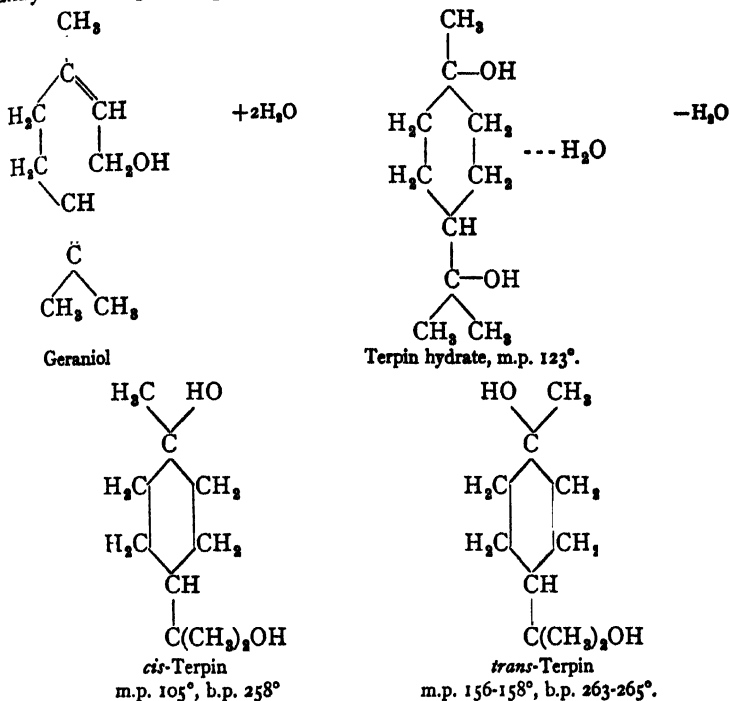
Owing to the presence of three asymmetric carbon atoms in the molecule, various isomeric forms of menthol are possible. The relative configurations of these compounds have been established by Read¹ (see p. 401). In the following formulæ $\text{Pr} = \text{C}_3\text{H}_7$. The elimination of water to form a Δ^8 -menthene occurs most readily with *neo*- and *neiso*-menthols, in which H and OH are in the *trans* position to one another



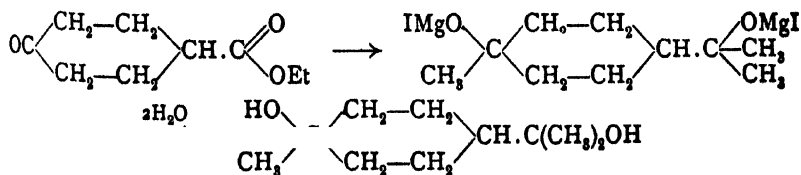
Among the technical methods for preparing the menthols may be mentioned the catalytic reduction of thymol which yields a mixture of (\pm)-menthol (45 per cent.), (\pm)-*neomenthol* (50 per cent.), and (\pm)-*isomenthol* (5 per cent.).

Terpin, 1:8-menthane-diol, $\text{C}_{10}\text{H}_{20}\text{O}_2$, exists in two stereoisomeric (*cis*- and *trans*-) forms. A crystalline hydrate of terpin, known as *terpin hydrate*, $\text{C}_{10}\text{H}_{20}\text{O}_2 + \text{H}_2\text{O}$, is produced when pinene or dipentene is allowed to stand for some time at the ordinary temperature in contact with dilute mineral acids. Terpin hydrate is also formed from geraniol

by treatment with dilute sulphuric acid. It forms colourless crystals, m.p. 116-117° (123° in a sealed-tube), which at the melting-point give anhydrous terpin, m.p. 104-105°.

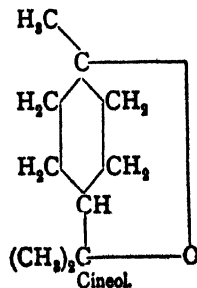


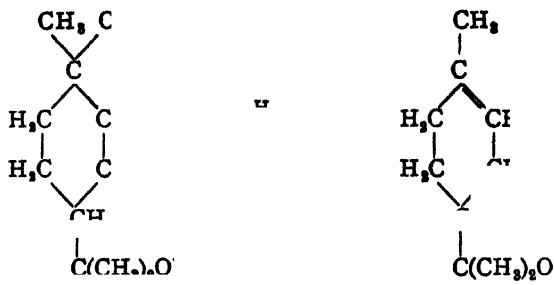
Perkin and Kay synthesised terpin by treating cyclohexanone-4-carboxylic ester with excess of methyl magnesium iodide, and have thus confirmed its constitution.



Cineol, of the annexed formula, is an inner anhydride of terpin, and occurs in many ethereal oils, such as oil of eucalyptus, wormseed oil and rosemary oil. It is a liquid of boiling-point 176°, with a smell of camphor. When treated with hydrochloric acid in glacial acetic acid solution, it is converted into dipentene dihydrochloride, $\text{C}_{10}\text{H}_{18}\text{Cl}_2$.

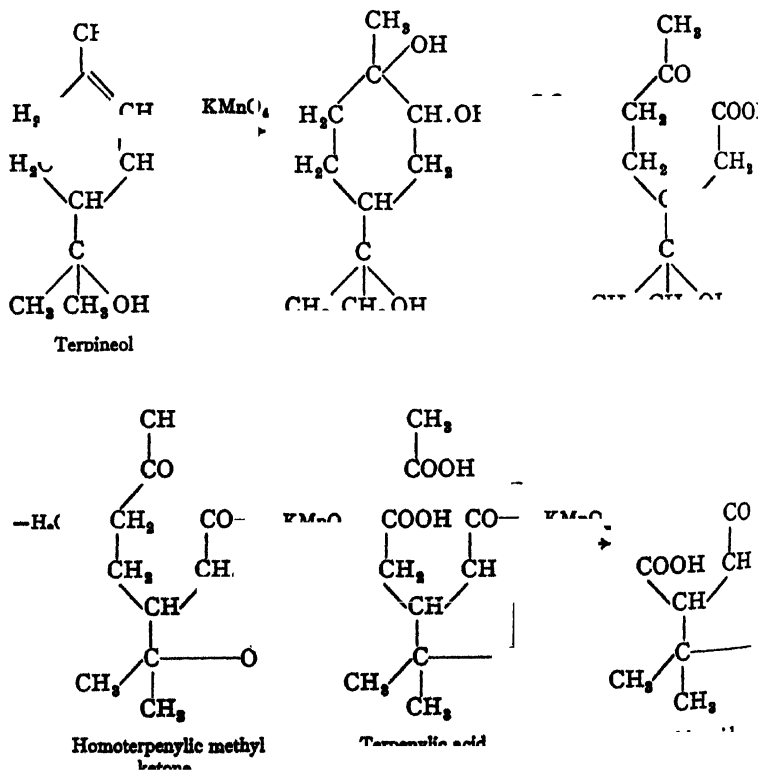
α -Terpineol, Δ^1 -menthen-8-ol; is a solid and occurs in many essential oils in the (+)-, (-)-, and (\pm)-forms. It is manufactured from α -pinene by hydration to terpin hydrate followed by careful dehydration of the latter.





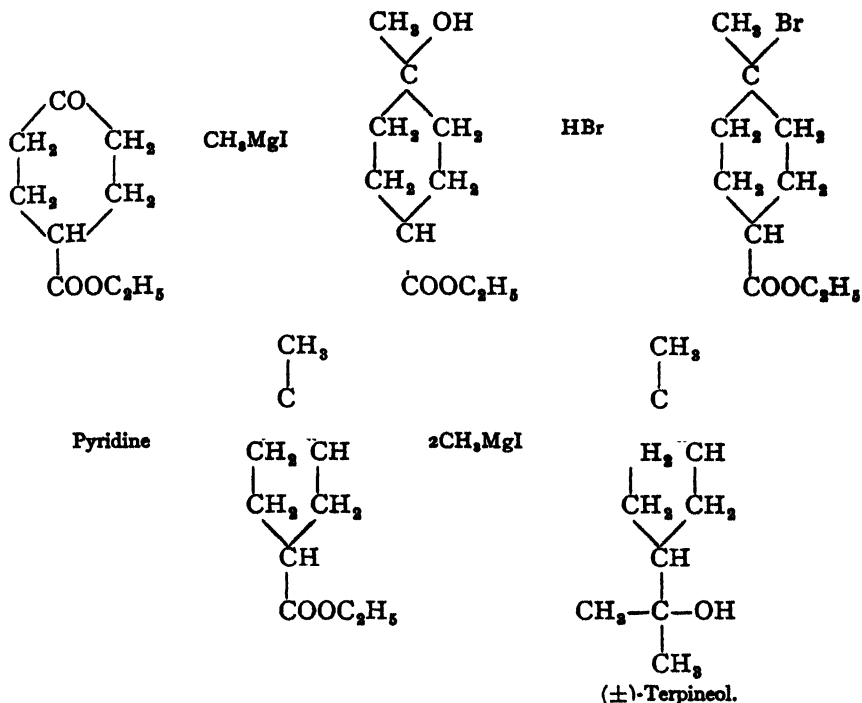
It has an odour of lilac and hence is used in the manufacture of perfume.

On dehydration with potassium bisulphate terpineol yields dipentene and with oxalic acid terpinolene, thus showing that it is a *p*-cymene derivative. It contains one double bond and one hydroxyl group, the positions of which were shown by graded oxidation.



Both terpenylic acid and terebic acid have been synthesised.

The structure of terpineol was confirmed by synthesis from cyclohexanone-4-carboxylic acid (W. H. Perkin, Jr.).

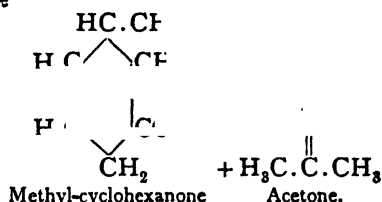
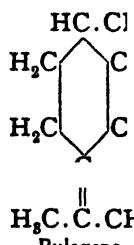
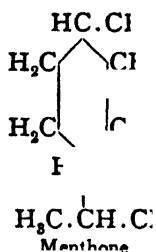


Among the ketones of this group are menthone, already described on p. 398, piperitone, pulegone and carvone. Buchu-camphor is an example of a ketonic alcohol.

Piperitone, Δ^1 -menthen-3-one, is an unsaturated ketone found in the (–)-form in a number of eucalyptus oils, especially in that of the Broad-leaved Peppermint (*E. Dives*). More recently a (+)-piperitone has been isolated by Simonsen from the essential oil of a Himalayan grass, *Andropogon Jwarancusa*. Piperitone has been carefully investigated by Read and his co-workers and in his hands has proved of great value in establishing the configurations of the menthones, menthols¹ and menthylamines. On hydrogenation it yields a mixture of menthone and isomenthone.

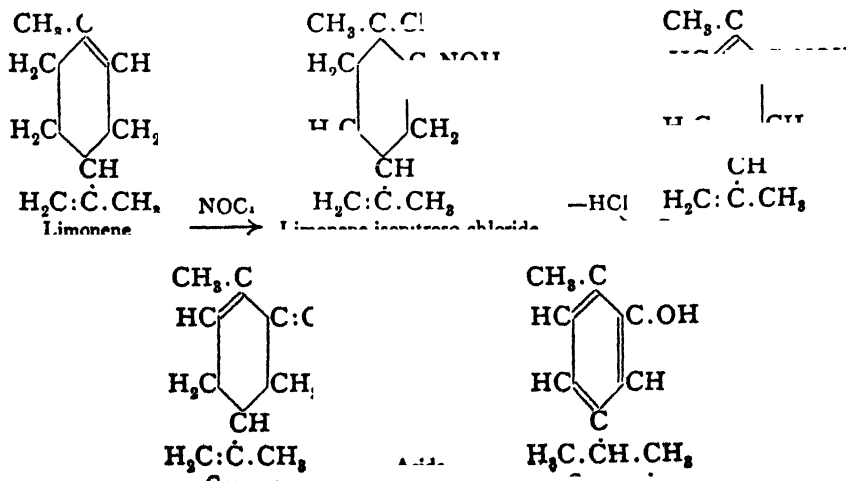
Pulegone, $\Delta^{4(8)}$ -menthen-3-one, b.p. 221°, is present in oil of pennyroyal. The keto-group occupies a similar position to that in menthone, into which compound pulegone may be converted by hydrogenation. When superheated with formic acid or water, pulegone is hydrolysed to 3-methyl-cyclohexanone and acetone, from which its constitution is deduced.

¹ See p. 398.

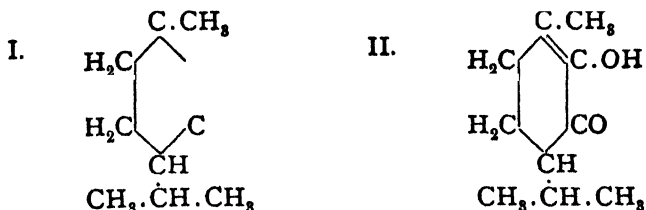


Pulegone reacts with hydroxylamine in the normal manner to form an oxime; it also yields an addition product in which hydroxylamine is attached to the unsaturated linking, the group $\text{C}=\text{C}$ being converted into $\text{CH}-\text{C}.\text{NHOH}$.

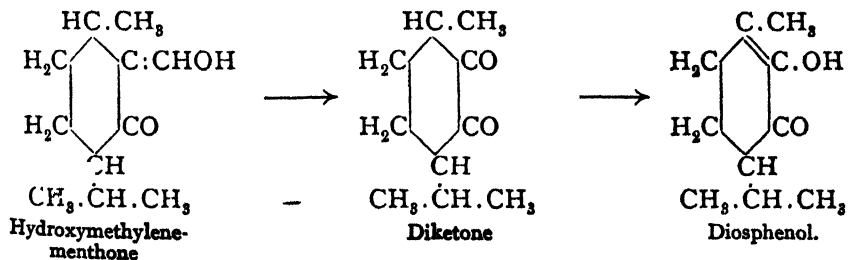
Carvone, $\Delta^{6:8}$ -*menthadiene-2-one*, formerly known as carvol, exists like limonene in (+)-, (−)- and (±)-modifications. (+)-Carvone (b.p. 230°) is the odorous and chief constituent of caraway oil. It gives the usual reactions of a ketone and contains two double bonds, since on reduction it gives the saturated alcohol tetrahydrocarveol (*carvo menthol*). It readily isomerises into carvacrol, the hydroxyl group of which has been shown to occupy the 2-position. This must also be the position of the carbonyl group of carvone. The double bond may be located from the close relationship existing between carvone and limonene, and has been established with certainty by the oxidative degradation of carvone.



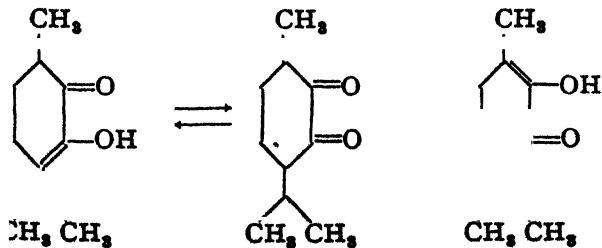
Diosphenol, *Buchu-camphor*, Δ^1 -menthen-2-ol-3-one, $C_{10}H_{18}O_2$, is prepared from an essential oil obtained from various kinds of the genus *Barosina* found in South Africa. It boils at 109° to 110° under 10 mm. pressure, and melts at 83° to 84° . One of the two oxygen atoms is contained in an alcoholic hydroxyl group, since the compound yields an acetate and a benzoate. The second is a ketonic oxygen atom, as diosphenol forms a normal oxime. Hence the substance is a ketonic alcohol. It has also been shown to be monocyclic and unsaturated. Oxidation with ozone leads to the production of α -isopropyl- γ -acetyl-*n*-butyric acid, thus proving the structure of that part of the molecule shown in I, (below). The arrangement of the remaining atoms is deduced from the reduction of diosphenol to the glycol, $C_{10}H_{20}O_2$, which on oxidation yields α -isopropyl- α' -methyl-adipic acid, thus showing the presence of a six-membered ring with methyl and isopropyl groups in the para-position to one another. The disposition of the ketonic and hydroxyl groups is now obvious. Further, it follows that the double bond must be attached to the carbon atom linked to the methyl group, the position 2 : 3 being impossible. Diosphenol therefore possesses the structure II.



Semmler and McKenzie synthesised diosphenol by oxidising hydroxy-methylene-menthone to a diketone which isomerised to diosphenol.



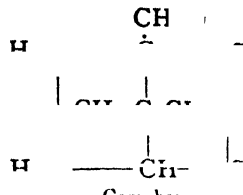
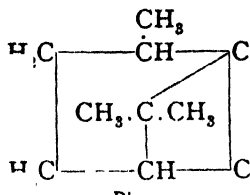
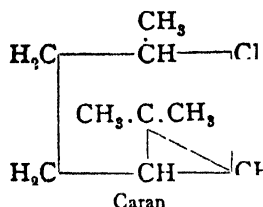
Diosphenol is probably a tautomeric compound,¹ and there is evidence that it reacts in the three forms shown below.



¹ J. Walker and J. Read, *J.*, 1934, 238.

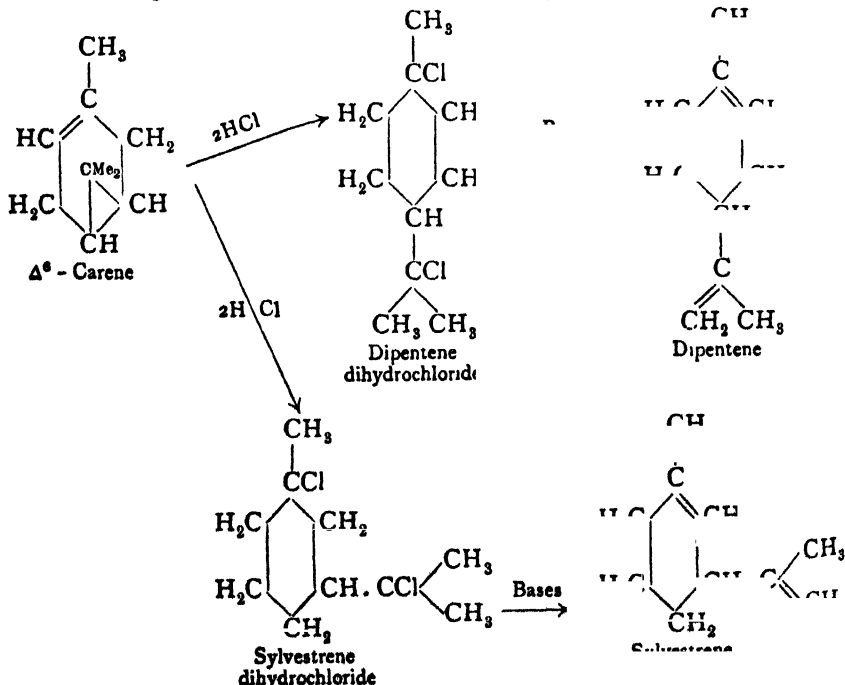
Dicyclic Terpenes and Camphor

The most important member of this class is ordinary or Japanese camphor. Before discussing this compound in detail, however, the parent hydrocarbons of the alcohols and ketones will be considered. Just as many of the monocyclic terpenes may be traced back to the saturated hydrocarbon menthane, the dicyclic terpenes and their derivatives may be referred, according to the type of "bridged-ring" present, to one of the three saturated hydrocarbons, carane, pinane and camphane.



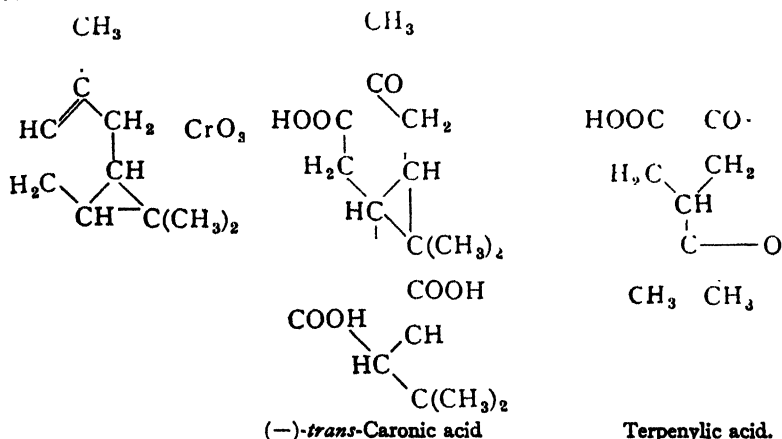
Dicyclic Terpenes

The dicyclic terpenes have been investigated by the methods which proved so rewarding in the mono-cyclic series. The chemistry of the dicyclic compounds, however, is made somewhat difficult by their tendency to isomerise into other ring systems, carane derivatives, for example isomerising into camphane derivatives and *vice versa*. Several examples of these changes will be encountered in the sequel



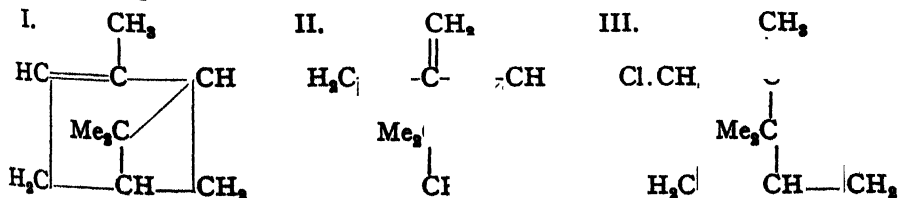
Carenes probably occur more widely in nature than was formerly supposed, but during the purification of the essential oils with hydrogen chloride they become transformed into dipentene dihydrochloride and sylvestrene dihydrochloride by the opening of the cyclopropane ring (*Simonsen*).

The structure of Δ^6 -carene was shown by oxidation with chromic acid to caronic acid and terpenylic acid.¹ Δ^1 -Carene has also been isolated.



α -Pinene (I, below).—Turpentine resin exudes in considerable quantities from firs, pines, and other conifers when incisions are made in the bark of the tree. By distillation in steam the resin is separated into volatile turpentine oil and non-volatile *colophonium* (*rosin*). *Oil of turpentine* is a colourless liquid, boiling-point 155° - 165° , and is a mixture. It absorbs oxygen from the air, becoming thick and finally resinifying.

The principal constituent of oil of turpentine is α -pinene, the most widely distributed of all the terpenes: in addition, a small quantity of an isomeride, β -pinene or *nopinene* (II) is found. Although these compounds differ in the position of the double bond, it is not possible to distinguish between them by means of simple addition reactions, because in many cases they yield the same products. With hydrogen chloride, for example each pinene gives bornyl chloride (III) and in presence of dilute sulphuric acid each is converted into the same terpin.

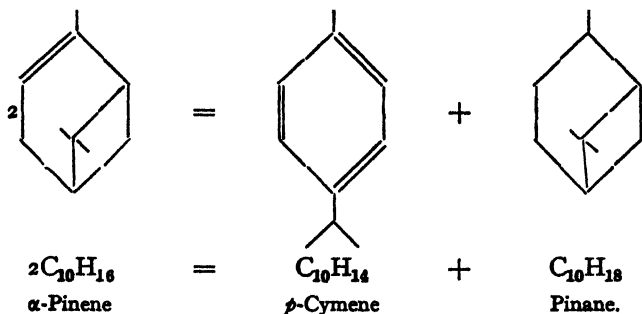


α -Pinene exists in optically active forms. (+)-Pinene is present in American, German, and Russian oil of turpentine, and (-)-pinene is found

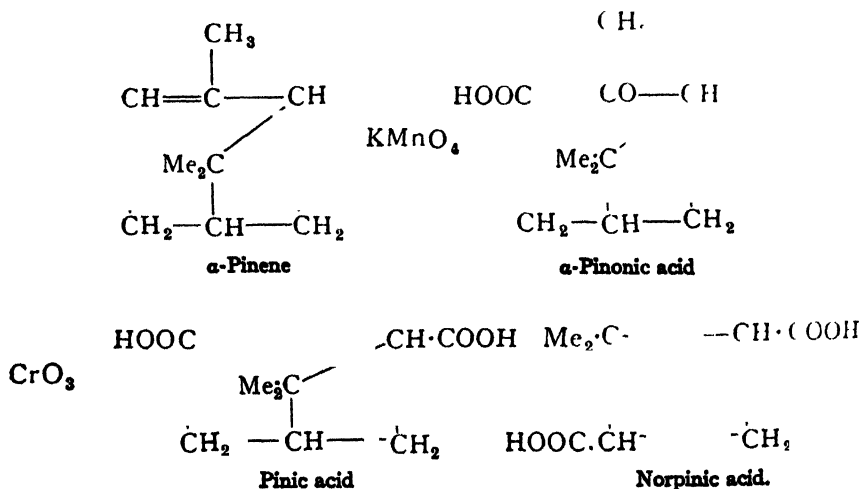
¹ J. L. Simonsen, *J.*, 1929, 305.

in French turpentine. An inactive pinene is obtained by the action of aniline on active pinene nitroso-chloride, when nitrosyl chloride is removed.

The structure of pinene has been determined by a number of reactions and a partial synthesis.¹ When boiled with platinum charcoal α -pinene undergoes disproportionation to yield *p*-cymene and pinane.²



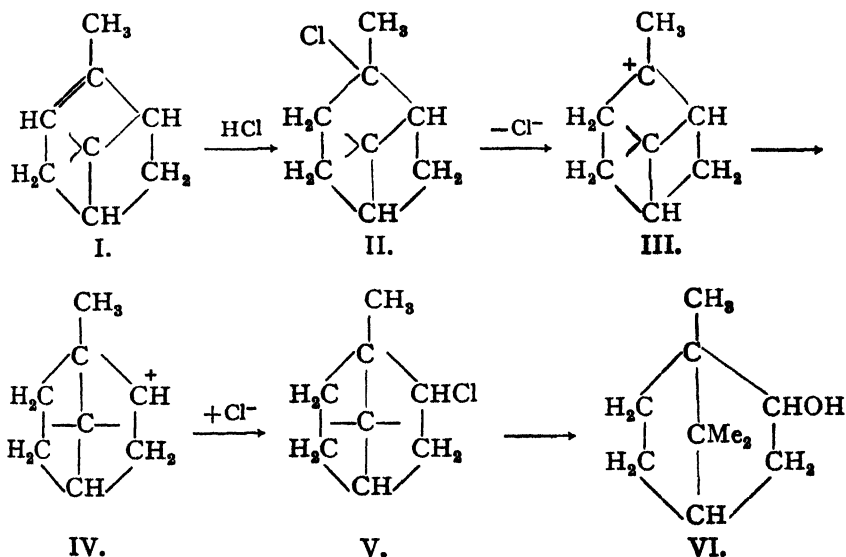
This relationship to *p*-cymene is confirmed by the formation of dipentene when pinene is treated with sulphuric acid. The presence of the cyclobutane ring is shown by oxidation to α -pinonic, pinic, and finally, norpinic acid.



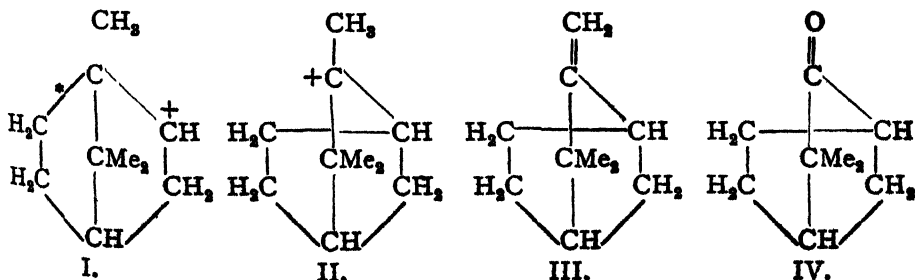
Dry hydrogen chloride led into well-cooled α -pinene (I) yields first pinene hydrochloride (II), which rapidly isomerises into bornyl chloride (V), a crystalline solid, m.p. 131-132°. Owing to its close resemblance to camphor in smell and appearance this substance is misnamed "artificial camphor". In the formation of bornyl chloride not only has the addition of hydrochloric acid taken place, but the carbon-skeleton has been altered

¹ L. Ruzicka and Trebler, *Helv. Chim. Acta*, 1921, 4, 666. ² R. P. Linstead, K. O. A. Michaelis and S. L. S. Thomas, *J.*, 1940, 1139.

and the "pinane bridge" changed into the "camphane bridge". This is confirmed by the fact that when the magnesium compound of bornyl chloride is treated with oxygen and the resulting product decomposed with dilute acids an almost theoretical yield of borneol (VI) is obtained. To this and similar changes the name *Wagner-Meerwein Transformation* is given (see p. 152). Investigation by a number of workers has shown that the reaction mechanism is essentially formation of a carbonium ion followed by a stabilising process (see also p. 554). Pinene hydrochloride (II) loses a chloride ion and gives the carbonium ion (III). Stabilisation is attained by migration of the bridge to give the carbonium ion (IV) with a camphane structure, and addition of a chloride ion to yield bornyl chloride (V).



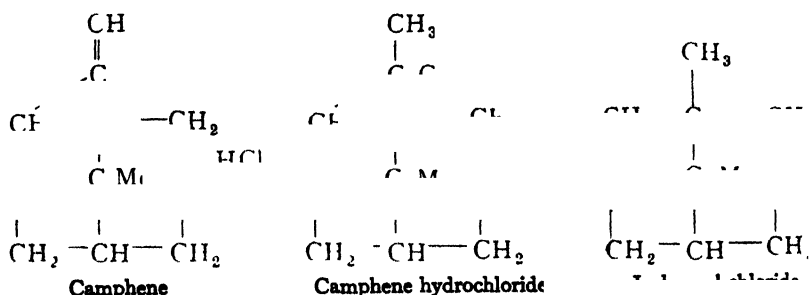
Camphene, $C_{10}H_{16}$, is a solid terpene (m.p. about 50°) found as the (+)-form in ginger, rosemary, and spike oils, and as the (–)-form in citronella and valerian oils. It has a smell of turpentine and camphor. Camphene is of interest as the only crystalline dicyclic hydrocarbon to occur in nature.



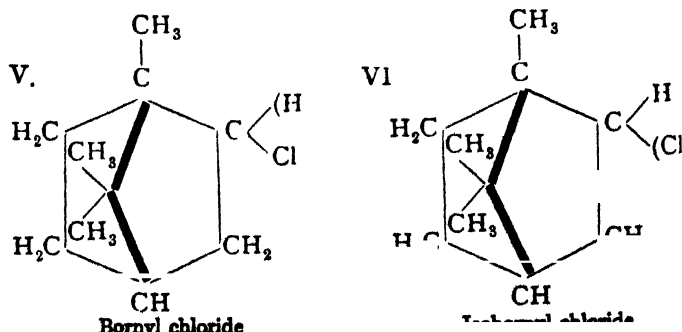
Camphene is prepared by heating bornyl chloride with the alkali, sodium phenate. Here again a Wagner-Meerwein transformation is involved. The bornyl chloride loses a chloride ion to give the carbonium ion (I), which is stabilised by migration of the two electrons forming the asterisk-marked bond to give the carbonium ion (II). Loss of a hydrogen ion affords camphene (III).

The above formula for camphene was first advanced by Wagner and is now generally accepted, though some of the reactions of the compound—for example, its oxidation to camphor and camphoric acid—are not explained by it. On the other hand the formula is supported by its ozonolysis to the ketone, *camphenilone* (IV), whose structure has been proved.

When hydrogen chloride is passed into an ethereal solution of camphene, *camphene hydrochloride* is obtained. This readily isomerises into isobornyl chloride. Here we have yet another example of the Wagner-Meerwein transformation.



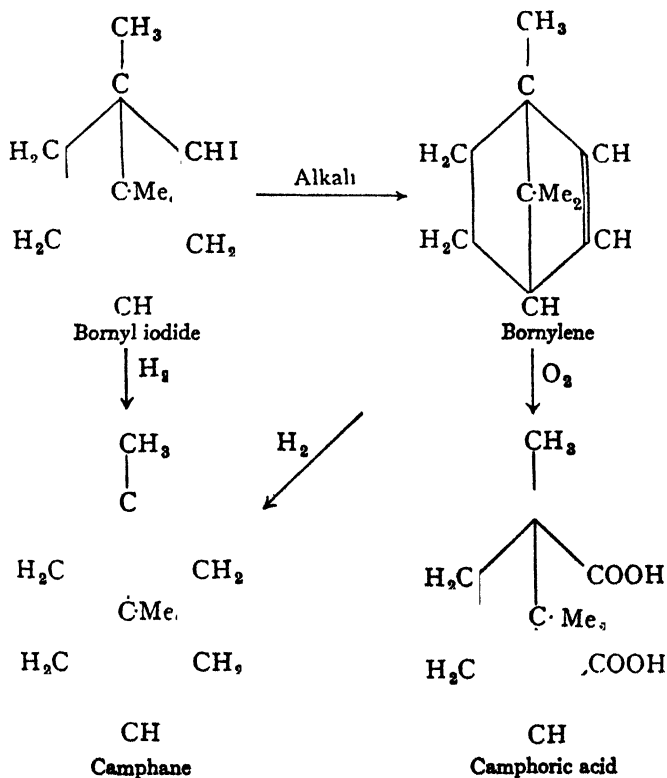
The isomerism of bornyl and isobornyl chlorides and of the corresponding alcohols, borneol and isoborneol, is readily explained as arising from the *cis* and *trans* position of chlorine or hydroxyl groups with respect to the $(\text{CH}_3)_2\text{C}=\text{CH}_2$ bridge across the cyclohexane ring (see formulæ (V) and (VI) in which the bracketed chlorine or hydroxyl is supposed to lie behind the plane of that part of the ring structure to



which it is attached). Although this problem has not been solved beyond dispute it appears probable that bornyl chloride and borneol are represented by *exo*-structures in which Cl or OH is in the *cis* position to the bridge, and that isobornyl chloride and isoborneol have the alternative *endo*-structures with a *trans* arrangement. Corresponding to bornyl and isobornyl chlorides are the two stereoisomeric secondary alcohols, *borneol* (formula V, p. 408) and *isoborneol*. Borneol with phosphorus pentachloride gives a mixture of bornyl and isobornyl chlorides; isobornyl alcohol gives only the isobornyl chloride.

Reduction of camphene at its double bond gives *isocamphane*.

Camphane.—As may be seen from its formula, camphane is



not directly related to camphene. An unsaturated derivative of camphane is *bornylene*, which may be prepared by treating bornyl iodide with alkali. Its structure is shown by oxidation to camphoric acid.

The structure of camphane follows from its formation by reduction of bornyl iodide or bornylene or decomposition of bornyl or isobornyl magnesium chloride with water. It possesses a symmetrical structure and is therefore optically inactive.

Alcohols and Ketones

Borneol, Borneo-camphor (formula V, p. 409), melts at 208° boils at 212° . It exists in nature in the (+)-, (-) and *r*-forms. (+)-*Borneol* is found in a tree, *Dryobalanops camphora*, growing in Sumatra and Borneo, and also in rosemary and spike oils; (-)-borneol and inactive variety occur in valerian oil. The formation of borneol from pinene and camphene hydrochlorides has already been described. It is related to ordinary camphor as a secondary alcohol to the corresponding ketone, and hence may be converted into camphor by oxidation with nitric acid or prepared from it by reduction with sodium and alcohol. Borneol resembles camphor in smell and burning taste. When warmed with potassium bisulphate it parts with water and yields camphene. *Isoborneol*, m.p. 212° , is a stereoisomeride of borneol which does not occur naturally; it may be obtained in the form of its acetate by warming camphene with glacial acetic acid and concentrated sulphuric acid at 50° to 60° . If isoborneol dissolved in xylene is treated with sodium it is transformed into *borneol*. With oxidising agents such as permanganate, ozone, chlorine or oxides of nitrogen, it is readily converted into camphor. The relationship between borneol and isoborneol has already been dealt with on p. 409.

Camphor, Japanese camphor, $C_{10}H_{16}O$, was until recently obtained exclusively from the camphor tree, *Laurus camphora*, growing in Japan (particularly in Formosa) and China but is now prepared industrially from turpentine by a series of reactions such as the following:—

Turpentine \rightarrow α -pinene \rightarrow bornyl chloride \rightarrow camphene \rightarrow isobornyl acetate \rightarrow isoborneol \rightarrow camphor.

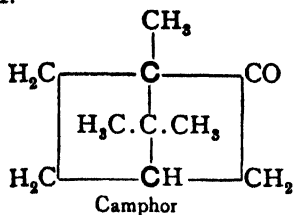
Many modifications of this process are to be found in the patent literature. In one process α -pinene is converted directly to camphor (U.S.A.), and in others camphene is oxidised to camphor.

It forms a colourless, transparent mass of characteristic smell and burning taste, m.p. 179° and b.p. 204° . In alcoholic solution it is dextrorotatory. The world's consumption of camphor is considerable since it is used in the manufacture of celluloid, explosives and perfumes and also in medicine.

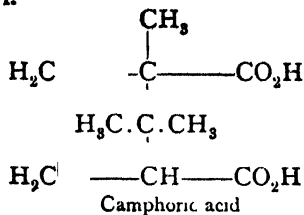
(-)-*Camphor*, occurs in the oil of *Matricaria parthenium*, and apart from the sign of its rotation, shows the same properties as ordinary camphor. By mixing the two antipodes, *r*-camphor, m.p. 178° , is obtained, identical with that produced by the oxidation of *r*-borneol or *r*-camphene.

Constitution of Camphor.—The first suggestion as to the constitution of camphor was advanced in 1859 by Berthelot, and for the next forty years numerous workers were engaged on the problem. Information was gained chiefly by the degradation of the camphor molecule by oxidation, and a series of detailed investigations on these lines finally led Bredt to put forward a constitution (formula VII) which is now generally accepted as correct.

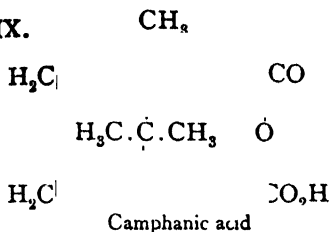
VII.



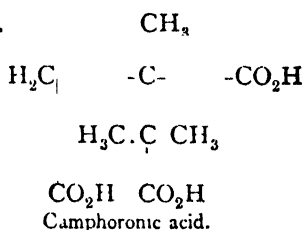
VIII.



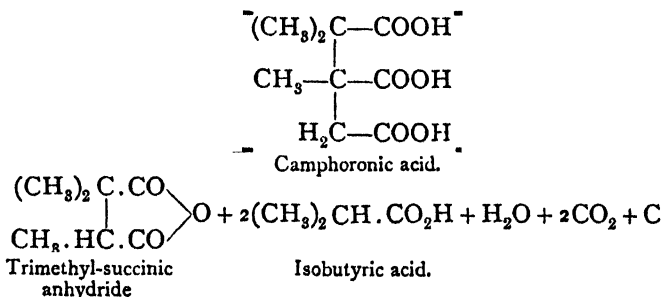
IX.



X.



The oxidation of camphor with nitric acid leads to the formation of *camphoric acid*, $\text{C}_{10}\text{H}_{16}\text{O}_4$ (VIII), *camphanic acid*, $\text{C}_{10}\text{H}_{14}\text{O}_4$ (IX), and *camphoronic acid*, $\text{C}_9\text{H}_{14}\text{O}_6$ (X), as chief products. These three

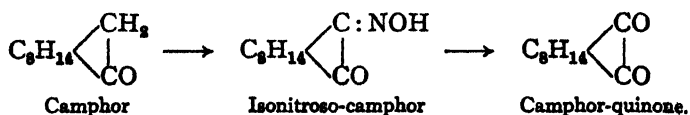


acids represent different stages of oxidation, and camphoronic acid itself may be obtained by the continued oxidation of either of the other two.

Two facts established by Brecht are of special significance in connection with the constitution of camphoronic acid. It is a tribasic acid which resembles tricarballic acid in its properties. On slow oxidation it breaks up mainly to form carbon dioxide, isobutyric acid and trimethyl-succinic acid. From this behaviour Brecht concluded that camphoronic acid was trimethyltricarballic acid, a view confirmed later by its synthesis by Perkin and Thorpe.

Since camphoronic acid is an oxidation product of camphanic acid, camphoric acid and camphor, it may be concluded that the carbon framework of camphoronic acid is present in each of these compounds, thus leading to the formulæ shown above. Trimethyl-succinic acid has also been prepared directly from camphoric acid by oxidation with chromic acid. The constitution of camphoric acid has in addition been confirmed synthetically (see p. 412).

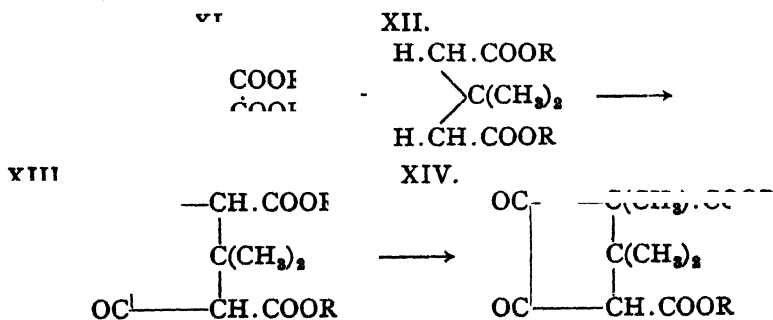
The ketonic character of camphor is proved by the formation of an oxime, $C_9H_{16} : C : NOH$, and the position of the CO-group is shown by the conversion of camphor into carvacrol, $C_{10}H_{14}O$ (see p. 505), on boiling with iodine. In the latter compound the hydroxyl is in the ortho-position to a methyl group. The presence of the group $CH_2.CO$ in camphor follows from the production of *isonitroso-camphor* on treatment with amyl nitrite and sodium alcoholate.



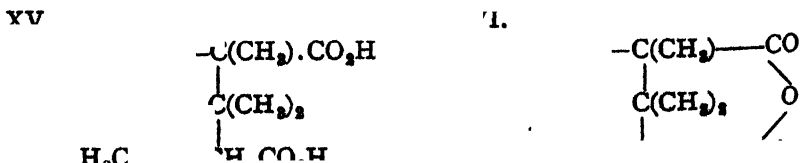
When this substance is boiled with dilute sulphuric acid it yields *camphorquinone*. The conversion of camphor to camphor-quinone is accomplished in one step by oxidation with selenium dioxide.

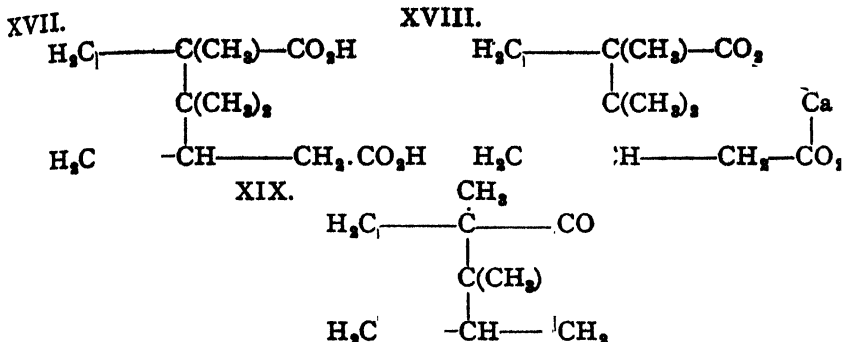
Among other reactions camphor yields *p*-cymene by loss of water when it is heated with P_2O_5 .

Synthesis of Camphor.—The most convincing proof of Bredt's formula for camphor is provided by Komppa's synthesis of camphoric acid, from which camphor itself had previously been obtained. The method employed was as follows: The dimethyl ester of $\beta\beta$ -dimethylglutaric acid (XII) was condensed with oxalic ester (XI) to give diketo-apocamphoric ester (XIII). From this, by treatment with metallic sodium and methylation with methyl iodide, was obtained diketo-camphoric ester (XIV), which by way of various intermediate compounds was reduced to *r*-camphoric acid (XV).



Camphoric anhydride, when treated with sodium amalgam, can also be converted into the lactone, campholide (XVI), which with potassium cyanide yields the nitrile of homocamphoric acid (XVII). The calcium salt of this acid (XVIII), on distillation, finally gives the corresponding ketone, camphor (XIX).

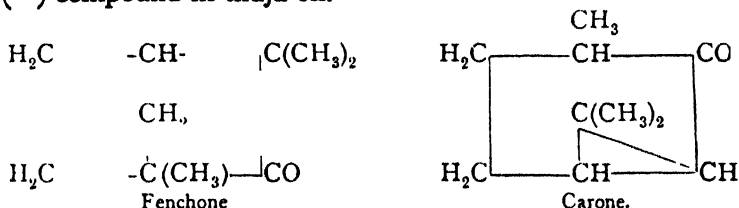




Another synthesis of camphoric acid was effected by Perkin and Thorpe.

Other ketonic derivatives of the dicyclic terpenes are fenchone and carone.

Fenchone, m.p. 5° , b.p. 192° to 194° , is very similar to camphor in its behaviour. It is found as the (+)-enantiomorph in fennel oil, and as the (—)-compound in thuja oil.



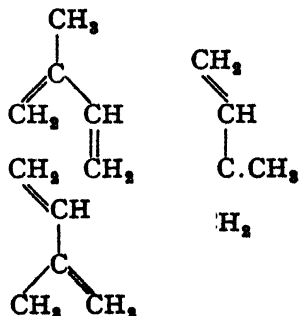
Carone (b.p. $100^\circ/15$ mm.) is a ketone derived from the hydrocarbon, arane. It does not occur naturally but can be prepared from carvone.

Sesquiterpenes and Diterpenes ¹

The sesquiterpenes include hydrocarbons of the formula $\text{C}_{15}\text{H}_{24}$ and their oxygen derivatives, and are found widely distributed in essential oils. The members of this group may be divided into *open-chain*, *monocyclic* and *dicyclic* compounds. Much of our knowledge is due to Ruzicka, Simonsen and others. They may be regarded as derived from three molecules of isoprene (Ruzicka), as may be seen by inspection of the formulæ of farnesol, bisabolene and zingiberine.

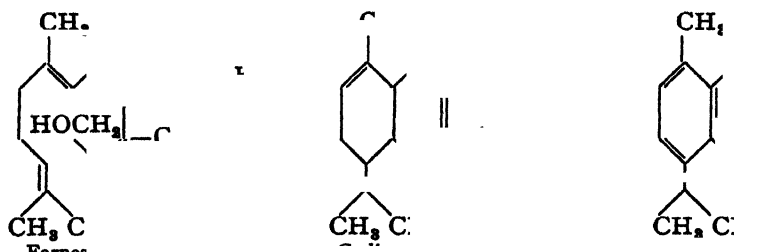
Among the methods successfully used in elucidating the structure of these terpenes are ozonisation, graded oxidation, and in the case of the cyclic compounds sulphur dehydrogenation (*Vesterberg* method) to naphthalene derivatives.

The relationship between the open-chain and cyclic sesquiterpenes may be illustrated by the conversion of the open-chain terpene *farnesol*



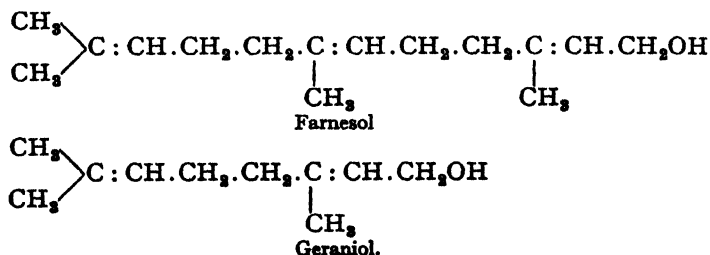
¹ L. Ruzicka, *Über Konstitution und Zusammenhänge in der Sesquiterpenreihe* (Berlin, 1928).

to the dicyclic hydrocarbon *cadinene*, which on dehydrogenation via *cadalene* (1 : 6-dimethyl-4-isopropyl-naphthalene)

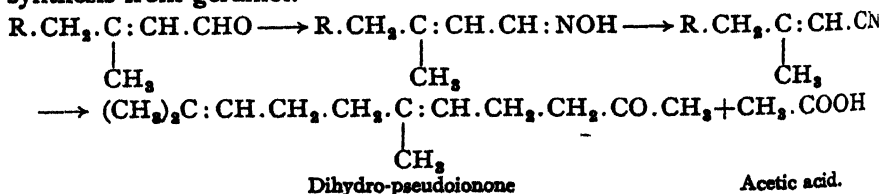


Open-chain Sesquiterpenes

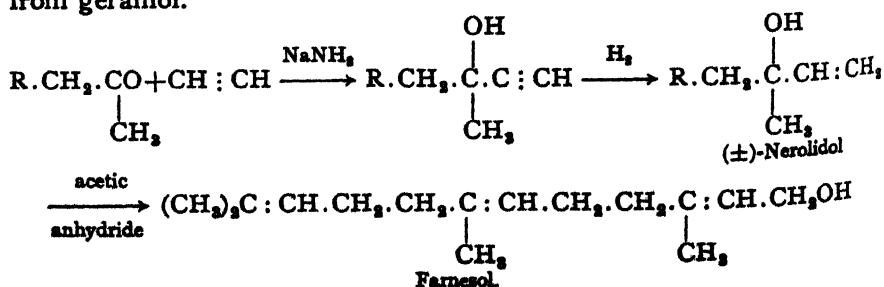
Farnesol is the constituent of many pleasant-smelling oils such as lily of the valley. Its structure follows from its relationship to geraniol from which it may be synthesised.



Farnesol can be oxidised to the corresponding aldehyde, *farnesal*, the oxime of which on elimination of water gives a nitrile. Hydrolysis of the nitrile yields in addition to the expected *farnesenic acid* a ketone dihydro-pseudoionone, the structure of which was established by its synthesis from geraniol.



Farnesol can be synthesised from this ketone and consequently from geraniol.



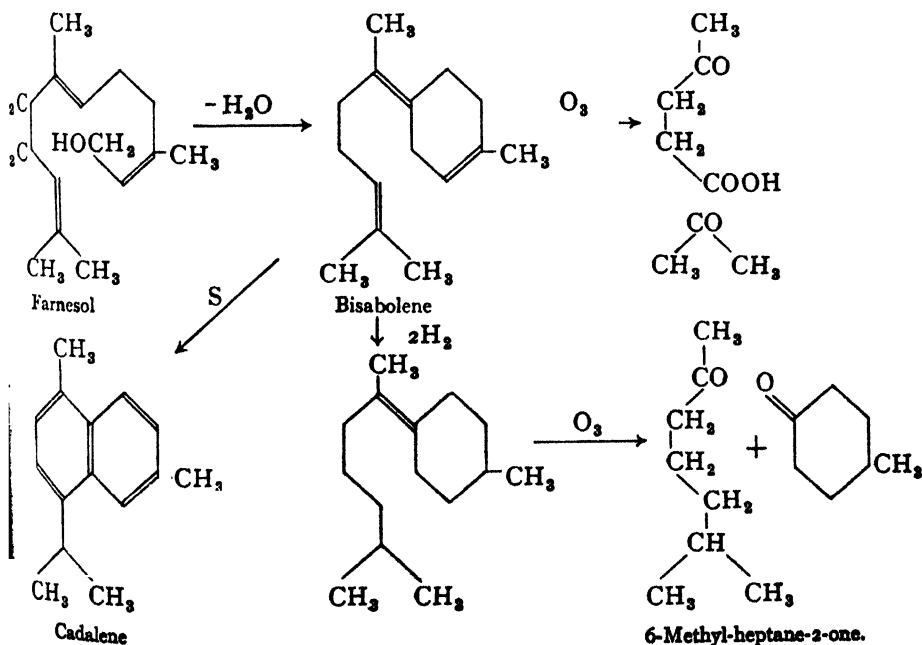
(\pm)-**Nerolidol**, the intermediate product obtained isomerises on treatment with acetic anhydride, a change reminiscent of the isomerisation of linalool into geraniol by the same reagent.

Monocyclic Sesquiterpenes

It has been found that just as the monocyclic terpenes are related to *p*-cymene so the cyclic sesquiterpenes may be regarded as derivatives of 1:6-dimethyl-4-isopropyl-naphthalene (*cadalene*) and 1-methyl-7-isopropyl-naphthalene (*eudalene*). In many cases these naphthalene compounds are obtained from the sesquiterpenes by sulphur dehydrogenation.

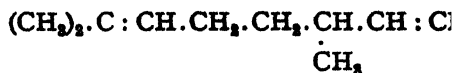
Bisabolene, a common constituent of essential oils, is obtained by the action of strong acids on farnesol. The structure of bisabolene follows from this reaction and others such as hydrogenation to hexahydro-bisabolene (3 mols. of hydrogen being absorbed); ozonisation to lævulinic acid and acetone; and sulphur dehydrogenation to cadalene.

The presence of a six-membered ring linked by a double bond to the rest of the molecule is proved by ozonisation of tetrahydrobisabolene to 4-methylcyclohexanone and 6-methylheptan-2-one.

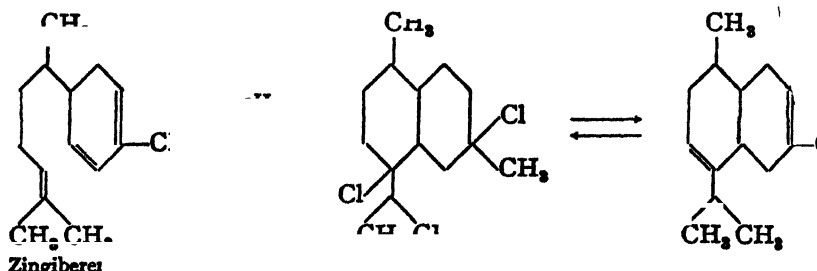


An isomer of bisabolene, **zingiberene**, occurs in oil of ginger. It reacts with two molecules of hydrochloric acid to give a di-hydrochloride, from which two molecules of hydrochloric acid can be removed to give the dicyclic compound *isosingiberene*, whose structure has been established

by methods similar to those applied to cadinene¹ (see p. 417). The formula for zingiberene has been established by interaction of the compound with dimethyl acetylenedicarboxylate and pyrolysis of the resulting Diels-Alder adduct.² The products are dimethyl 4-methylphthalate and 2 : 6-dimethylocta-2 : 7-diene,

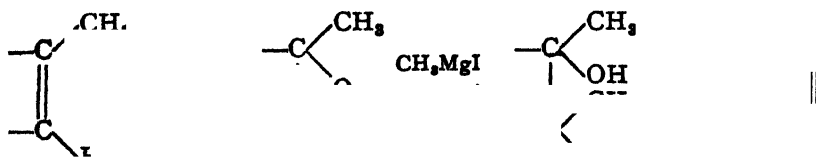


thereby showing clearly the structure of zingiberene.



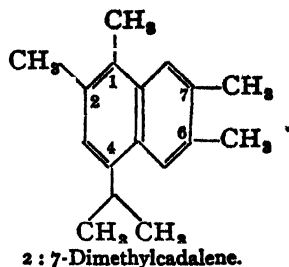
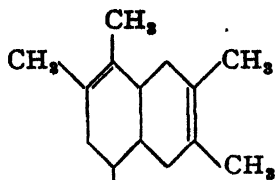
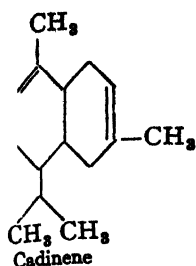
Dicyclic Sesquiterpenes

Cadinene, which occurs in oil of cubebs, is the most widely distributed dicyclic sesquiterpene. As already stated it can be prepared from farnesol, and on dehydrogenation with sulphur or selenium it yields cadalene. Its structure has been shown to be $\Delta^{1:6}$ -1 : 6-dimethylisopropyl-hexahydronaphthalene, the positions of the double bond being established by the following method.³ The compound is converted into mono- and di-oxides by perbenzoic acid and the points of attack "marked" by interaction of the oxides with methyl magnesium chloride to give methyl- and dimethylcadinenes.

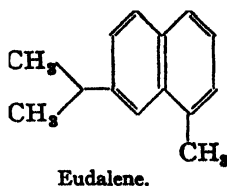
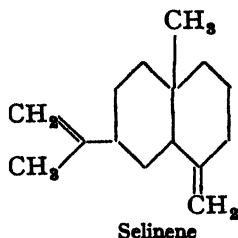


The dimethylcadinene on dehydrogenation gives 1 : 2 : 6 : 7-tetramethyl-4-isopropyl-naphthalene (2 : 7-dimethylcadalene), the constitution of which was determined by synthesis. The double bonds in cadinene are therefore in the 1 : 2- and 6 : 7-positions.

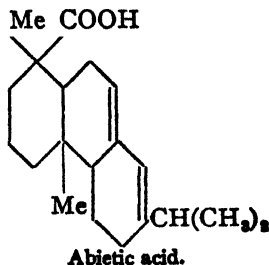
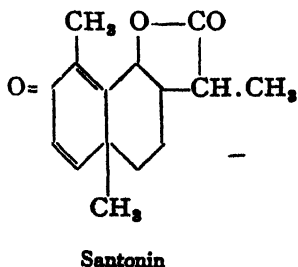
¹ M. D. Soffer, C. Steinhardt, G. Turner, M. E. Stebbins, *J.A.C.S.*, 1944, 66, 1520.
² A. Eschenmoser and H. Schinz, *Helv. Chim. Acta*, 1950, 33, 171. See also S. M. Mukherjee and N. K. Bhattacharyya, *J.A.C.S.*, 1953, 75, 4698.
³ W. P. Campbell and M. D. Soffer, *J.A.C.S.*, 1942, 64, 147.



Some dicyclic sesquiterpenes are derivatives of eudalene, 1-methyl-7-isopropylnaphthalene, into which they are converted by sulphur dehydrogenation. **Selinene**, from celery oil, is a member of this group. When heated with sulphur it gives eudalene, the process involving not only the loss of hydrogen but also of a methyl group as methyl sulphide—a sign that selinene contains an angular methyl group.



Santonin, C₁₅H₁₈O₈, m.p. 170°, [α]_D = -171°, is the active constituent of wormseed (*Artemisia Santonica*). Clemo and Haworth¹ have shown it possesses the annexed formula. It is thus a lactone closely related to the eudesmol group of terpenes.



Diterpenes and Triterpenes

Comparatively little is known about the diterpenes, C₂₀H₃₂, which occur chiefly in vegetable resins and balsams. The best-known representative is the carboxylic acid, **abietic acid**, C₂₀H₃₀O₂, which forms the chief constituent of ordinary rosin (*colophonium*). When heated with

¹ G. R. Clemo, R. D. Haworth, and E. Walton, *J.*, 1929, 989; 1930, 1110. G. R. Clemo and R. D. Haworth, *ibid.*, 1930, 2579.

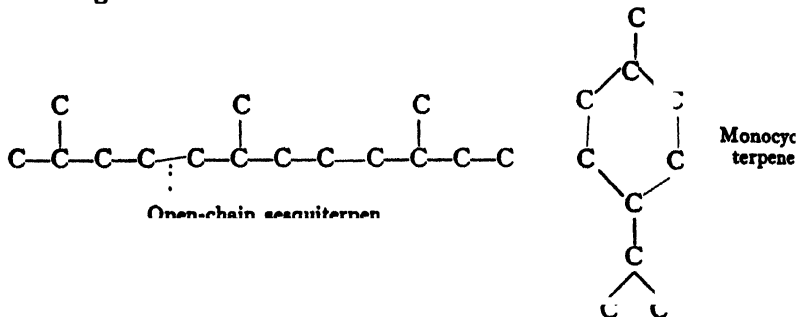
sulphur, abietic acid yields retene, 1-methyl-7-isopropyl-phenanthrene. The accepted formula for abietic acid is given on p. 417.¹

Squalene,² $C_{30}H_{50}$, is an open-chain dihydro-triterpene obtained from the livers of certain fish. Its structure has been elucidated by synthesis.³



Isoprene and Terpene Structure

With very few exceptions all terpenes of known constitution, whether simple or complex, open-chain or cyclic, have been found to possess a molecular structure built up of a complete number of isoprene units. According to this "isoprene rule" the terpenes are composed of isoprene units arranged in "head to tail" fashion.



This relationship possibly indicates a common origin in the form of some reactive 5-carbon compound such as isovaleraldehyde, $(CH_3)_2CH \cdot CH_2 \cdot CHO$, or of simpler products which may give rise to it, a speculation which is supported by the occurrence of isovaleraldehyde (and of acetone and acetaldehyde) in a number of essential oils. It has been suggested that these substances by condensation and reduction may give rise to citral or geraniol and thus to various more complex derivatives.⁴

RUBBER

Rubber is obtained from the sap of a number of trees belonging to the *Apocynaceae*, *Moraceae* and *Euphorbiaceae* families. These are found in tropical countries, particularly in South America, Africa and the East Indies. The most valuable rubber tree is the *Hevea brasiliensis*. The bark of the tree is "tapped" by making a small incision and the milky latex which oozes out is collected in pans. The latex is next polymerised, e.g. by subjecting it to the action of smoke, to give crude rubber. This is freed from admixed sand, bark and other impurities by boiling with

¹ For an excellent account of the determination of the structure of abietic acid see F. S. Spring, *Ann. Reports*, 1941, 187. ² Heilbron and co-workers, *J.*, 1926, 1630, 3131; 1929, 873, 883.

³ P. Karrer and A. Helfenstein, *Helv. Chim. Acta*, 1931, 14, 78. ⁴ Compare Kremers, *J. Biol. Chem.*, 1922, 40, 21. I. Read, *Chem. Rev.*, 1920, 9, 1. Hall, *ibid.*, 1933, 23, 479.

water, when the mass becomes plastic. It is then kneaded between warm rollers until homogeneous, and finally rolled out into sheets. The product so obtained consists essentially of caoutchouc, the hydrocarbon constituent of rubber. It has no definite melting point, is insoluble in water, dilute acids and alkalis, but dissolves in benzene, carbon disulphide and chloroform. On dry distillation it yields isoprene (p. 128). With N_2O_3 the various forms of caoutchouc are generally converted into a nitrosite of the composition $(C_{10}H_{16}N_2O_7)_2$, a reaction which may be used technically for the quantitative estimation of rubber in rubber goods.

Distillation of Caoutchouc.—When subjected to dry distillation rubber decomposes to give a mixture of products, the more volatile of which boil as low as 25° , whilst others range above 300° . Of these products only two fractions have been carefully investigated, namely those boiling at 30° to 40° and 160° to 170° respectively. In the latter fraction is found *dipentene* (Wallach), and in the former *isoprene*, *dimethyl-allene* and *dihydro-isoprene*. This problem has been very largely cleared up by the work of Ipatieff, who also showed that isoprene could only be prepared in the pure state by indirect methods. The constitution of isoprene has been established by the syntheses of Euler and Ipatieff. Harries found that from 1500 gms. of good caoutchouc only 35 gms. of isoprene boiling at 33° to 34° could be obtained.

Synthesis of Rubber.—The first real synthesis of rubber is due to Tilden in 1892, who discovered that a sample of isoprene, prepared by heating dipentene, had in the course of some months polymerised into rubber. The technical application of this polymerisation was discovered independently in 1910 by Matthews and Harries, who showed that isoprene on being warmed for about 50 hours to 60° with sodium wire in a sealed tube, is practically quantitatively converted into a solid rubber. Harries showed that the polymerisation could also be effected, though less satisfactorily, by heating isoprene with glacial acetic acid to a temperature above 100° in a sealed tube. In this connection it has to be borne in mind that synthetic rubber is not identical with the natural product.

Constitution of Caoutchouc.—The molecular constitution of caoutchouc has not yet been solved, largely owing to the difficulties presented by its high molecular weight and peculiar physical properties, which render purification a difficult problem. Any suggested structure must conform to the following experimental facts.

1. Caoutchouc has the empirical formula $(C_8H_8)_n$, although the most highly purified samples so far prepared still have traces of N, O and S.

2. It is optically inactive and therefore probably contains no asymmetric carbon atom.

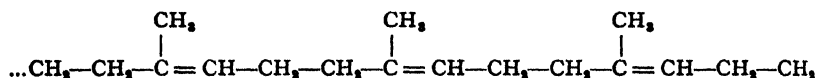
3. It appears to be a complex polymeride of isoprene, and yields a so-called *tetrabromide*, $(C_{10}H_{16}Br_4)_n$, and an *osonide*, $(C_{10}H_{16}O_4)_n$. Hence the molecule has two double bonds for every ten carbon atoms (Harries).

4. The ozonide when boiled with water yields l  vulinic aldehyde and its peroxide, together with l  vulinic acid as a secondary oxidation product (Harries).

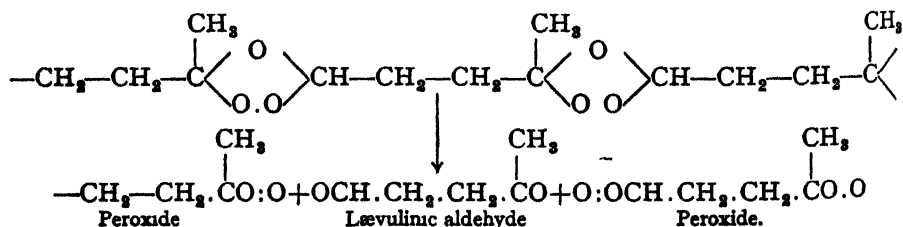
5. Hydrogenation experiments show that two hydrogen atoms are taken up for every eight already present.

Pummerer in 1929 determined the molecular weight of highly purified caoutchouc in menthol and in camphor solution, using the cryoscopic method. The results indicated $(C_5H_8)_n$, where $n=16$ to 24, thus giving a molar weight of 1100 to 1600. Measurements of viscosity carried out by Staudinger, on the other hand, led him to assign n as high a value as 1300.

Any formula for caoutchouc must retain isoprene as the unit of structure in order to account for the production of l  vulinic aldehyde on ozonisation, and of isoprene among other products of distillation. Further, the molecule would appear to be cyclic in view of the low percentage of hydrogen and degree of unsaturation. Pickle proposed a closed chain structure built up of an indeterminate number of C_5H_8 molecules.



Polymerisation is here represented as being purely chemical in nature, the union of isoprene molecules being accompanied by a rearrangement of the double bonds. The ozonide is assumed to be formed as a result of the separation of the carbon atoms at the points originally occupied by the double bonds, with the production of a compound having as its basis the following arrangement :



Water brings about decomposition of the ozonide at the points shown, with the formation of l  vulinic aldehyde, l  vulinic aldehyde peroxide, and some l  vulinic acid as a further oxidation product of the aldehyde. An arrangement of the above type is also advocated by Staudinger, who prefers, however, an open-chain formula.

It will thus be seen that the evidence bearing on the constitution of rubber is not conclusive. The possibility that it contains a mixture of polyterpene isomerides is supported by its indefinite physical characteristics as well as by the fact that isoprene, for example, may be polymerised

by various agencies such as ultra-violet light, hydrogen chloride, acetic acid and sodium, to form products whose properties depend to some extent upon the agent employed.

Guttapercha strongly resembles rubber and is prepared from the sap of certain plants (Sapotaceae) found in Malacca and the East Indies. It is purified in a similar manner to rubber, and is extensively used for making moulds, as insulating material, etc. Guttapercha is also derived structurally from isoprene, and Staudinger has suggested that this compound and caoutchouc are represented by similar formulæ, differing chiefly in the arrangement of the groups around the double bonds, the former having a *cis* and the latter a *trans* configuration (*see also* p. 426).

Vulcanisation of Rubber.—Caoutchouc is remarkable for its great elasticity, but with rise of temperature it gradually loses this valuable property, and on being cooled it becomes hard. To minimise these defects the great bulk of the rubber used industrially is vulcanised, a process which also renders it stronger, more elastic and practically insoluble in the usual solvents. **Hot vulcanisation**, discovered in 1839 by Goodyear, is effected by mixing the dry material with sulphur and other ingredients, such as fillers, accelerators and anti-oxidants, and heating at 120–160°. Soft rubber goods made in this way contain from 3–10 per cent. of sulphur, hard rubber goods from 10 to 35 per cent. If the proportion of sulphur rises to 25–35 per cent., **ebonite** or **vulcanite** is formed, a hard product used as insulating material. Selenium has also been utilised for vulcanisation, generally in admixture with sulphur.

For special purposes **cold vulcanisation** is employed, involving immersion in sulphur monochloride, S_2Cl_2 , dissolved in carbon disulphide or other suitable solvent. This method was introduced by Parkes in 1846, and is used for thin goods such as surgeon's gloves. Sulphur chloride may also be applied in the form of vapour. A recent special process for thin rubber, due to Peachey, is to submit it to the action of gaseous sulphur dioxide, followed after a period by hydrogen sulphide. Finely divided and highly reactive sulphur is thus deposited in the material, causing vulcanisation to proceed at ordinary temperatures. This method is not much used.

As will be seen later, raw rubber has a macromolecular structure of long open or possibly closed chains, built up from isoprene units and containing one double bond for every five carbon atoms. Such chains are comparatively readily separated from one another by solvents. In soft vulcanised rubber the greater part of the sulphur is merely adsorbed, but the remaining atoms have entered into combination at some of the points originally occupied by the double bonds¹ so as to form cross links which unite the chains laterally. The presence of thioether links can be proved by their additive reaction towards methyl iodide, which can be used as a means of estimating the proportion of sulphur bridges in a given sample.² It is this change in the molecular pattern which modifies

¹ See, for example, K. H. Meyer and W. Hohenemser, *Helv.*, 1935, 18, 1061. ² Meyer and Mark, *Ber.*, 1928, 61, 1928.

the physical properties, giving greater rigidity and resistance to solvents. In ebonite the process has been carried so far that the bulk of the sulphur is in the combined state. The resulting hard product has an empirical formula approximating to C_8H_8S , and thus contains one atom of sulphur for each double bond present in the original raw rubber.

Accelerators.—In the absence of accelerators vulcanisation proceeds slowly. Until 1906 the only compounds added to speed up the reaction were metallic oxides, principally litharge, white lead, lime or magnesia. In that year Onslager discovered that organic amines were also effective and these are now used, often mixed with inorganic oxides. Among compounds of this type may be mentioned antimony sulphide, Sb_2S_3 , hexamethylene tetramine, thiocarbanilide and a variety of dithiocarbamates and xanthogenates. In addition to reducing the time or lowering the temperature required for vulcanisation, the use of accelerators frequently improves the quality of the product, giving increased strength and greater resistance to abrasion.

Fillers are blended in a finely divided state with the "mix" in order to modify the stiffness, strength or other properties of the finished product. They may stiffen the vulcanised rubber without increasing the total energy necessary to extend a strip to the breaking point. Whiting, barytes and ground slate are used in this manner. On the other hand, "reinforcing" pigments may be added which lead to an increased energy being required to extend a strip to the breaking point. Carbon black is thus used in large proportions in the manufacture of motor tyres. Zinc oxide and magnesium carbonate are added for the same purpose.

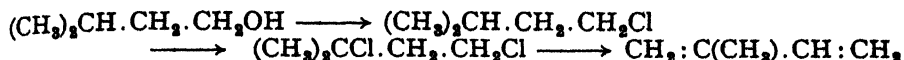
Anti-oxidants are introduced into the mix in small quantities (0.5 to 2 per cent.) in order to delay oxidation and ageing of the rubber in light and air, which result in hardening, flex-cracking and loss of tensile strength. This is a later development of rubber technology, but already a very large number of compounds have been suggested and used for the purpose. Thus amines and amino-phenols, aldehyde amines, amino-ketones and their condensation products and various absorbents of ultra-violet light have been utilised. Raw rubber contains a considerable amount of a natural anti-oxidant which protects it from rapid deterioration, but the quantity present is insufficient for the protection of the rubber in the vulcanised state.

Synthetic Rubbers¹

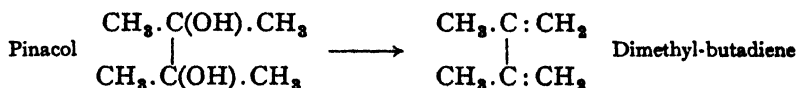
Polymerisation methods enable us to convert many hydrocarbons containing conjugated double bonds into rubber-like products. Industrial processes for preparing isoprene, butadiene, etc., are therefore of great interest and importance. Some of these are summarised below. It may be noted that the first two are now of historical importance only.

¹ See *Synthetic Rubber*, by W. J. S. Naunton (Macmillan, 1937). Also *Synthetic Rubber and Plastics*, E. A. Hauser, *J. Chem. Ed.*, 1944, 21, 15. *Natural and Synthetic Rubbers*, H. L. Fisher. *J. Chem. Ed.*, 1942, 19, 522.

Isoprene can be obtained from fusel oil (isoamyl alcohol) by treatment with hydrochloric acid to form isoamyl chloride, followed by chlorination to a dichloro-pentane. On being passed over soda lime at 470° , this last loses hydrogen chloride and yields isoprene.

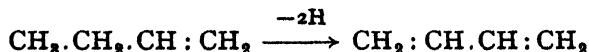


Dimethyl-butadiene is prepared from starch as the raw material. In the Fernbach process starch is converted into acetone by fermentation using a special anaerobic micro-organism. The acetone is then reduced with aluminium foil to pinacol, which in contact with alumina at 400° loses water to form dimethyl-butadiene.

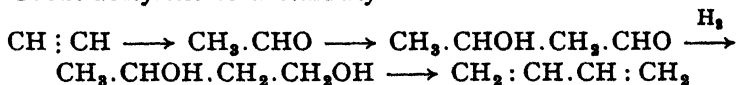


Butadiene is manufactured in a variety of ways of which the following are the most important :—

(1) Much of the butadiene manufactured in the U.S.A. is obtained by the dehydrogenation of butylenes in presence of a catalyst.



(2) From acetylene or acetaldehyde

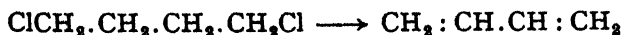


In America large quantities of acetaldehyde are also obtained by the oxidation of ethyl alcohol.

In Russia alcohol prepared from grain or potatoes is converted into butadiene by a catalytic method due to Lebedev (1933). The superheated vapour of crude alcohol is passed through an electrically heated chamber packed with oxides of aluminium and zinc.



(3) Removal of hydrochloric acid from dichlorobutanes prepared by the action of chlorine on butane or butylenes.

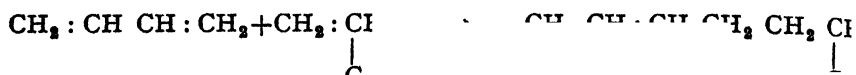


It is estimated that the butadiene manufactured in the U.S.A. for synthetic rubber is 440,000 tons per year.

Synthetic Rubbers.—The term synthetic rubber is used incorrectly : rubber has not yet been synthesised. It is so widely used, however, to designate substances with rubber-like properties that it will not in all probability be replaced by some other, possibly more cumbersome, term.

Most of the Russian synthetic rubber and much of the German is based on the polymerisation of butadiene, the products being different

types of *Buna rubber*. Rubber of this class is also made in the United States, where enormous quantities of **Buna S** are prepared to supplement the supply of natural rubber. **Buna S**—Bu for butadiene, Na sodium (polymerising agent), and S for styrene—is the chief synthetic rubber at present produced in the U.S.A. and is a *co-polymer* produced by interpolymerisation of butadiene and styrene...



Buna S

Buna S is generally compounded with carbon black and may be vulcanised with sulphur. It is the synthetic most similar to natural rubber and is the synthetic tyre rubber of the immediate future.

Some idea of the miraculous achievement of American chemists and engineers in establishing the synthetic rubber industry may be obtained from the following table :—

Estimated Production of Synthetic Rubber in the U.S.A. in 1944

	Tons
Buna S	765,000
Buna N	24,500
Butyl	26,200
Neoprene	53,200

Buna N is a co-polymer of butadiene and acrylonitrile and is excellent when resistance to oil or organic solvents is important.



Buna N

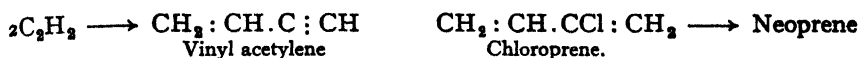
In these products the long macro-molecules of polymerised butadiene are assumed to be cross-connected by shorter links built up from styrene or acrylic nitrile, resulting in a considerable modification of the structural pattern. The interpolymers are more rigid, respond less to heat treatment, are resistant to solvents and are more difficult to work up. A property of technical importance is their greater resistance to abrasion and oxidation.

Polymerisation is effected by use of sodium (about 0.5 per cent) deposited on an iron wire comb, at a temperature not above 65° and over a period of about 90-120 hours. This is followed by a "ripening" period of 3-8 days at 40°. The yield under optimum conditions rises to 83 per cent.

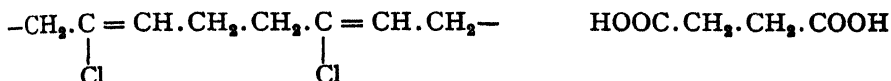
Emulsion polymerisation is more convenient for the production of interpolymers such as **Buna S** and **Buna N**. Thus a mixture of butadiene with 10 to 30 per cent. of acrylic nitrile is emulsified with a 5 per cent.

aqueous solution of the hydrochloride of diethylamino-ethyloleamide, containing a small amount of trichloroacetic acid. Polymerisation is quantitative in 3-4 days at 50-60°.

Neoprene, duprene is a rubber-like material containing chlorine, which has been developed in America. Acetylene is first submitted to controlled polymerisation in the presence of aqueous cuprous chloride to give vinyl-acetylene. From this by reaction with hydrogen chloride is obtained *chloroprene* (chlorobutadiene) which is polymerised by emulsifying in water containing suitable catalysts.

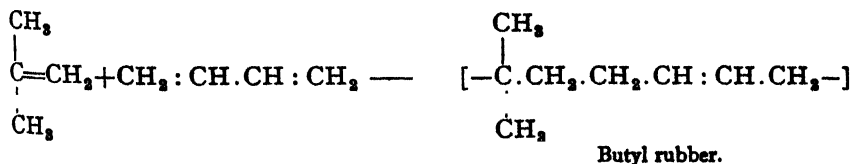


On oxidation with nitric acid neoprene yields succinic acid.¹ This is in agreement with the structure given below, and with its X-ray diagram.



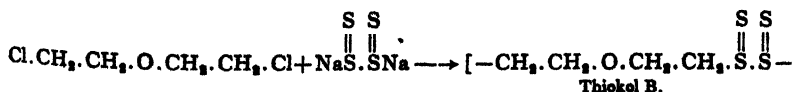
Neoprene is an elastic product which before it is worked up resembles smoked sheet rubber in appearance. It does not require vulcanisation, but is compounded with other suitable ingredients such as magnesia, wood rosin and zinc oxide prior to being made into manufactured articles. Neoprene is superior to natural rubber in its resistance to oils, heat, light and ozone, and is less permeable to gases. Although more costly than rubber it is therefore used for making transmission belts, printing rollers and flexible tubing employed for the conveyance of oil and petrol.

Butyl rubber is a co-polymer of isobutylene and small quantities of di-olefins such as isoprene or butadiene.



It can be quickly prepared at low cost, but its performance is not so good as that of Buna S. It has excellent chemical resistant properties.

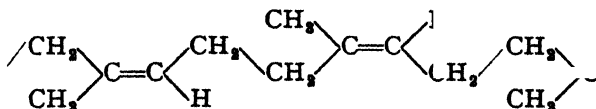
Lastly, the **Thiokols** may be mentioned as they have better resistance to aromatic hydrocarbons than rubber or the other synthetics. **Thiokol B** is made from dichloroethyl ether and sodium tetrasulphide.



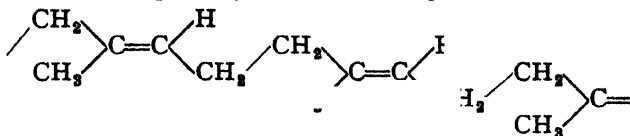
¹ W. H. Carothers, I. Williams, A. M. Collins and J. E. Kirby, *J.A.C.S.*, 1931, 53, 4208.

X-ray Analysis of Natural and Synthetic Rubbers

In 1925 it was observed by Katz¹ that when a piece of clear unvulcanised natural rubber is strongly stretched it becomes opalescent and gives an interference fibre diagram if examined by means of X-rays. Subsequent work by K. H. Meyer,² who used stretched films of rubber, showed that the distance between repeating units in the fibre axis corresponded to two isoprene residues, from which it was deduced that the CH_3 groups occupy *cis* positions about the double bonds.



Similarly, it is concluded that guttapercha³ is the corresponding *trans*-isomer, with a repeating unit of one isoprene residue.



The majority of the synthetic rubbers fail to give any definite X-ray diagrams on being stretched, probably because of irregularities arising from cross-linking of the fibres. An exception is found in neoprene, which Kenney³ found an identity period along the fibre axis corresponding closely to one isoprene unit. Neoprene therefore probably possesses the *trans* configuration, similar to that of guttapercha but with chlorine atoms replacing the methyl groups.

III

Introduction to the Aromatic Series

DRY DISTILLATION OF COAL AND MANUFACTURE OF COAL GAS

The main source of benzene and its methyl-homologues was formerly the tar obtained as a by-product when coal is submitted to dry distillation at temperatures above 1000°C ., either for the manufacture of coal gas or of coke for metallurgical purposes. In the former process gas coals are employed, rich in hydrogen and yielding a high proportion of gas, whereas in coke ovens a coal poorer in hydrogen is utilised, which will give a good yield of a dense coke. Gas coke of open texture is, in addition, produced in relatively small amount in the manufacture of coal gas, and gas is also obtained from the coke ovens. Coal tar and an aqueous liquor containing ammonia (gas liquor) are obtained as by-products in both processes.

¹ *Naturwiss.*, 1925, 23, 410.

² K. H. Meyer and H. Mark, *Ber.*, 1928, 61, 1939.

³ A. W. Kenney, *I.A.C.S.*, 1931, 22, 4207.

The distillation of gas coal is carried out in retorts of fireproof clay. Volatile products of decomposition are led through pipes to a trough, in which the bulk of the tar condenses. Coal gas passes on, and is freed from further quantities of tar and ammoniacal gas liquor by passage through specially constructed chambers which are well cooled with water. The remainder of the ammonia is removed by washing the gas in water. The gas is next freed from hydrogen cyanide, usually by washing with a solution of an iron salt, the resulting cyanogen compounds of iron being subsequently worked up for potassium ferrocyanide and other products. Finally, sulphur is removed, generally by leading the gas through cast-iron chambers containing hydrated ferric oxide spread out in thin layers.

The purified coal gas is collected over water in gas-holders or gasometers, and delivered under pressure into distributing pipes. It contains hydrogen (about 50 per cent. by volume), methane (35 per cent.) and carbon monoxide (8 per cent.) as non-luminous constituents, and ethylene, acetylene, benzene and naphthalene (totalling about 4 per cent.) as luminous constituents, together with carbon dioxide (1 per cent.), nitrogen (4 per cent.), hydrogen sulphide and ammonia as impurities.

From 100 kilos of coal are obtained on the average 27 to 30 cubic metres of gas, 5 kilos tar, 64 kilos coke and 100 kilos of ammoniacal gas liquor. In recent years, however, great quantities of benzene and toluene have been obtained by "stripping" coal gas.

Up to the present time the distillation of coal by the above process has usually been so conducted that the primary products of distillation are—by contact with the red-hot walls of the retort—largely converted into compounds of an aromatic nature, which collect in the tar. According to recent investigations the **low temperature distillation of coal** may be effected at 600° under reduced pressure, to give a large primary *distillate of aliphatic character*. In this manner the typical products of the petroleum industry may be prepared from coal (see p. 117).

The yield of tar from the low temperature process varies, according to the starting material, from 8 to 12 parts as against the 4 to 5 parts obtained from the ordinary process in the manufacture of coal gas. The low temperature tar may be prepared either as the chief product of distillation in apparatus designed to this end, or as a by-product from the gas generator.

Coal Tar

Properties, Composition and Uses.—Coal tar as obtained from the manufacture of coal gas or the coke ovens is a black, viscous liquid of peculiar acrid smell. It contains at least 220 constituents of which according to A. E. Coulson 68 have been separated at one time or another on the industrial scale. These substances may be roughly divided into those of acidic, basic and neutral character. Among neutral products the most important are the hydrocarbons of the aromatic series—benzene and its homologues, naphthalene and anthracene, etc.—to which the

industrial value of coal tar is mainly due. Some idea of the products isolated from coal tar distillation may be obtained from the following analysis of a coke-oven tar¹ :—

	Percentage
Crude benzene and	1.1
Xylenes and cumen	1.5
Indene, coumarone,	1.1
Naphthalene .	1.1
α -Methylnaphthalen	1.1
β -Methylnaphthalen	1.1
Dimethylnaphthalen	1.1
Acenaphthene .	1.1
Fluorene . .	1.1
Anthracene . .	1.1
Phenanthrene .	1.1
Carbazole, etc. .	1.1
Phenol . . .	1.1
Cresols, xylenols, et	1.1
Pyridine, etc. .	1.1
Oily mixtures .	1.1

The nature and percentage of the products obtained depend on the coal tar used. For instance, the percentage of benzene and toluene is frequently higher than in the above table, 1.1 - 1.5 per cent. being a common figure.

Coal tar, with the exception of petroleum and cellulose, is probably put to a greater variety of uses than any other substance. In the crude state, without any previous rectification, it is used for protecting the surface of masonry and wood, for impregnating wood, in the preparation of composition roofing, in the manufacture of lampblack and briquettes, and as fuel. Its chief value, however, lies in its distillation products of which more than 200 have been isolated and identified.

In the past the isolation of chemicals from coal tar has been inefficiently carried out, but, with increased research on the subject, a great increase in the production of indene, cyclopentadiene, xylenols, picolines, etc., from coal tar may be expected.

Distillation of Coal Tar.—Distillation is carried out in roomy stills which are bricked in, and the distillate is condensed in an iron coil condenser. Four fractions are usually collected as follows :—

1. *Light oil*, which is lighter than water and distils between 80° and 170°.
2. *Middle or carbolic oil*, sp. gr. approximately 1, which distils between 170° and 240°.
3. *Heavy or creosote oil*, which is heavier than water and distils between 240° and 270°.

¹ Quoted by D. D. Miller in *Chemical Age*, 1944, 51, 603.

4. *Green or anthracene oil*, which is green in colour and distils between 270° and 400° .

The *pitch* which is left as a residue in the retort is utilised in the preparation of varnish and lacquer, briquettes and other products.

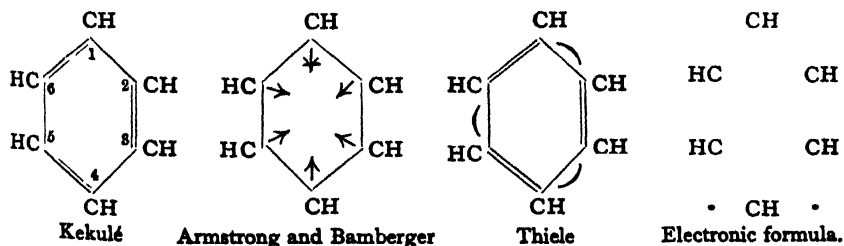
For the production of benzene hydrocarbons the only fraction of importance is the light oil. This is washed with aqueous sodium hydroxide to remove acids, and with concentrated sulphuric acid to remove bases, and is then fractionated in a rectifying column. Benzene, toluene, $C_6H_5 \cdot CH_3$, and xylenes or dimethyl-benzenes, $C_6H_4(CH_3)_2$, are thus obtained in a relatively pure form, and are placed directly on the market.

CONSTITUTION OF BENZENE

A very large number of compounds is derived from the hydrocarbon benzene, C_6H_6 , many of which are of great importance industrially. Certain of these substances were obtained originally from aromatic oils and resins, and as they were of unknown constitution and possessed a pleasant odour, they were classed together as *aromatic compounds*. This term is now reserved for benzene derivatives.

The constitution of benzene has formed one of the most controversial topics in the history of organic chemistry, and even now, after a century of experiment and speculation, the problem cannot be regarded as completely solved. We have seen that the chemical behaviour of aliphatic substances in general is adequately expressed by means of formulæ compounded of single, double, and triple bonds. In benzene and other aromatic compounds, however, the carbon-carbon linkages are neither single nor double bonds and indeed are not readily pictured in terms of the simple concepts of classical organic chemistry. We shall return to the problem later.

In 1865 Kekulé¹ as the result of brilliant intuition proposed for benzene a regular hexagonal formula in which each carbon atom is linked to one hydrogen atom. Almost all subsequent formulæ have been modifications of Kekulé's idea.



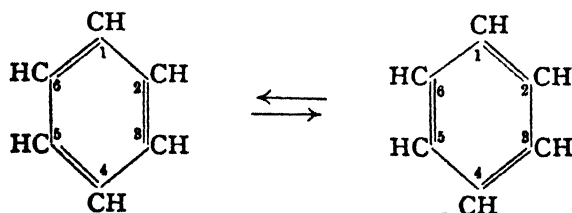
In proposing his formula for benzene, Kekulé² was guided by two regularities already established in connection with the chemistry of aromatic substances. Each benzene compound derived from the hydrocarbon by the replacement of one atom of hydrogen by another atom or

¹ *Bull.*, 1865, 1, 98. *Ann.*, 1866, 137, 129.

² Kekulé, *Ann.*, 1866, 137, 129.

radical existed in one form only. On the other hand, each di-substitution product of benzene occurred in three isomeric forms. From the first of these statements it followed that the six hydrogen atoms of benzene are chemically equivalent to one another, as was later shown conclusively by Ladenburg. Accordingly, the benzene formula should have each of the six hydrogen atoms attached in a similar manner to carbon, a condition which is fulfilled by the formulæ $C_6(CH_2)_2$, $C_3(CH_2)_3$, and $(CH)_6$. Of these, however, only the last satisfies the second condition, that three isomeric di-substitution products should be possible. Hence Kekulé came to the conclusion that benzene must contain a closed chain of six carbon atoms, to each of which is attached one hydrogen atom. A doubtful point in this formula is the position of the fourth valency of the carbon atoms. Kekulé suggested that each carbon was linked to one of its two neighbours by a double bond, thus arriving at the above formula for benzene.

Kekulé's formula, however, does not satisfy all the requirements. It was first pointed out by Ladenburg that the existence of four structurally isomeric di-substitution products would be expected from a structure of this kind, whereas, as already mentioned, the observed number is always three. In addition to the three di-derivatives represented by the positions 1 : 2, 1 : 3, and 1 : 4, there would be expected, according to the Kekulé formula, a fourth isomer of the type 1 : 6, since this differs from the 1 : 2 position in the arrangement of the double bond. By means of a further hypothesis Kekulé was able to bring his formula into harmony with the experimental facts. The single and double bonds were assumed to oscillate rapidly between the alternative positions as shown in the following formulæ :



On this view any distinction between positions 1 : 2 and 1 : 6 disappears, and the occurrence of more than three di-substitution products is impossible.

It is interesting to note that Kekulé, when he advanced his formula, was unaware of reactions in which benzene behaves as a triene. It was only later that such reactions were discovered in the formation of a triozone, the catalytic hydrogenation to cyclohexane, and the catalytic oxidation of benzene vapour to maleic anhydride, although Faraday in 1825 had shown that chlorine under suitable conditions can form a hexachloride by the addition of three molecules of chlorine to benzene.

Kekulé's theory of oscillating single and double bonds did not meet with universal acceptance and other formulæ such as those of Armstrong and Bamberger, Thiele, etc., were proposed. These formulæ have been discarded, but they merit attention since they foreshadowed recent developments which demand six identical carbon-carbon linkages in benzene. Thiele's application of his partial valency theory, for example, represents benzene as containing "six inactive double-bonds" and thus explains the almost completely saturated properties of the benzene ring. Reference has already been made on p. 14 to his work on compounds containing conjugated double bonds, as the result of which he put forward the hypothesis that the affinities in the ordinary double bond were not completely utilised, but left residual or "partial valencies" in excess. When two double bonds are in the conjugated position, the residual valencies on the two central atoms are supposed mutually to satisfy one another. This conception when applied to the closed system of conjugated double bonds in the Kekulé formula for benzene, leads to the conclusion that the residual affinities of the double bonds are completely saturated, as expressed in Thiele's formula on p. 529, and Thiele's theory of the stability of benzene, in its original form at any rate, has been discarded, but the modern theory now accepted (see below) may be regarded as Thiele's theory with the vague "partial valencies" replaced by precisely defined electrons and electron movements.

The main argument against the Kekulé formula, as modified by the oscillation hypothesis, is the fact that in its chemical properties benzene is much less unsaturated than the olefins, and resembles rather the hydrocarbons of the saturated series. Halogens, for example, unite only with difficulty with benzene, whereas they combine instantaneously with aliphatic compounds containing multiple bonds. Benzene is very stable towards ordinary oxidising agents and does not react with alkaline potassium permanganate, which is a specific reagent for ethylene derivatives.

The physical evidence is equally emphatic that the benzene ring does not contain olefinic bonds. For example, the double bonds of aliphatic and alicyclic substances are readily hydrogenated with evolution of heat. Ethylene and cyclohexene, for instance, have a heat of hydrogenation per double bond of 32.58 and 28.59 Kcal. respectively. In conformity with these values, cyclohex-1:3-diene yields cyclohexane with evolution of 55.37 Kcal., but benzene when hydrogenated to cyclohexane loses only 49.80 Kcal. It follows that when benzene is hydrogenated with one molecule of hydrogen to give cyclohex-1:3-diene instead of the expected evolution of heat 5.57 Kcal. are absorbed. The reaction is endothermic instead of exothermic. Clearly the bonds of benzene are fundamentally different from those associated with normal olefinic linkages.

Further insight into the nature of the benzene bonds comes from accurate measurements of the lengths of these bonds. Kathleen Lonsdale

from X-ray investigations on crystalline hexamethylbenzene showed that the six carbon atoms of the ring lie in one plane and that the molecule possesses a centre of symmetry. In other words all the carbon-carbon distances (1.39 Å) in the molecule are equal. A similar conclusion was reached by Ingold and his co-workers from infra-red and Raman spectra measurements on the vapours of benzene and deuterated benzene. Now it has been established from measurements of many substances that a single carbon-carbon linkage has a length of 1.54 Å and a double bond 1.33 Å. The Kekulé formula would therefore require the bonds of the benzene ring to alternate between 1.54 and 1.33 Å, a result quite incompatible with the above experimental results.

The most adequate explanation of the chemical and physical anomalies of benzene has been provided by the quantum mechanic picture of the carbon atom and by the theory of resonance. As has been already shown (see p. 24), one stable configuration of the carbon atom has three electrons (σ -electrons) at an angle of 120° to one another in a plane containing the carbon nucleus. The fourth electron (a π -electron) moves in an dumb-bell orbital at right angles to this plane. The first three electrons are obviously "ready-made" to form the benzene nucleus with its C—C—C and C—C—H angles of 120° . The π -electrons are then found in dumb-bell orbitals at right angles to the plane of the ring and are represented for simplicity in fig. 1 by their symmetry axes. Each of these orbitals overlaps contiguous orbitals with the result that they are no longer localised. The π -electrons thus "swarm" round the whole molecule and may be considered to be moving round the ring in either direction. This has been confirmed by the *magnetic anisotropy* of benzene. If a magnetic field is applied in a direction perpendicular to the plane of the ring the π -electrons will tend to move in one direction resulting in marked diamagnetism. This has been verified experimentally.

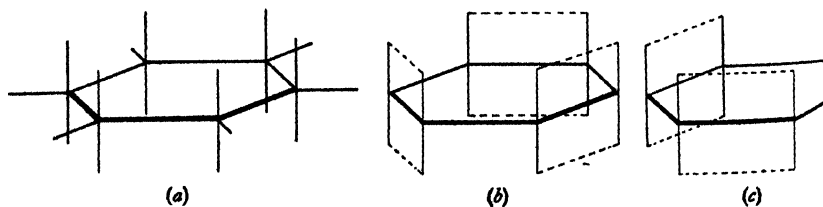


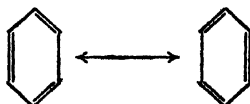
FIG. 1.

The molecular orbital theory of the benzene ring in no way resembles Kekulé's oscillating structures each with alternating single and double bonds. It shows a single structure in which all the bonds are equivalent and exist not as double or single bonds but as intermediates between the two. The delocalisation of the π -electrons has a further effect. They have a lower total energy than when paired in localised bonds, and consequently the molecule is stabilised by the delocalisation energy, what is more commonly termed the *resonance energy*.

The picture thus obtained of the benzene ring succeeds where previous models failed, namely, in accounting both for the symmetry and the stability of the benzene molecule.

The resonance of the molecule has been shown by accurate measurements of the heats of hydrogenation of benzene and its derivatives.¹ Tetrahydrobenzene and a molecule of hydrogen give cyclohexane and 28.6 Kcal. of heat. The hydrogenation of dihydrobenzene to cyclohexane is, as would be expected, accompanied by evolution of twice this quantity of heat, namely, 55.4 Kcal. If benzene were simply a triene with three double bonds its reduction to cyclohexane should be accompanied by a loss of about 84 Kcal. of heat. The observed heat of hydrogenation, however, is only 48 Kcal. showing that benzene has been stabilised by resonance to an extent of 36 Kcal.

In the valency-bond theory benzene is represented as a resonance hybrid with the Kekulé structures as the main contributing forms. This does not give the clear physical picture provided by the molecular orbital



method, but it is extremely useful particularly when applied to polycyclic aromatic hydrocarbons and their derivatives. It cannot be emphasised too strongly that benzene is in no sense a mixture of these two forms, but is a *combination* or *blending* of them.

Formula 1a is unserviceable for "everyday use", but fortunately the Kekulé formula may still be used. This is understandable if in chemical reactions the resonating molecule is excited into a transition state in which the electrons are localised (1b and 1c) and the Kekulé structures so produced then undergo chemical change. In all probability these two changes will occur simultaneously just as in many reactions the breaking of old bonds and the formation of new bonds occur concurrently.

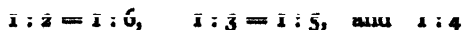
SUBSTITUTION IN THE BENZENE SERIES

If one of the hydrogen atoms in benzene be replaced by another element or radical, the resulting *mono-substitution product exists in one form only*. There is thus only one monochloro-benzene, C_6H_5Cl , one monoamino-benzene, $C_6H_5NH_2$, and so on. In other words owing to the equivalence of the six hydrogen atoms it is immaterial which position is assigned to the substituent.

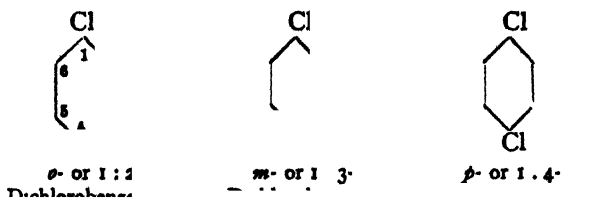
If two hydrogen atoms of benzene are replaced by two monovalent elements or radicals, the relative positions of the substituents greatly influence the properties of the compound.

¹ Kistiakowski *et al.*, *J.A.C.S.*, 1935, 57, 65, 876, etc. See also p. 431 of text.

All di-substitution products exist in three isomeric forms. If we indicate the position of the first substituent with the figure 1, the three compounds formed by the introduction of a second substituent may be written as follows :

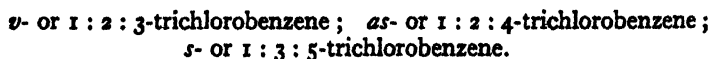


The derivative formed by substitution in position 2 or 6 is known as an *ortho*-compound, that in position 3 or 5 as a *meta*-compound, and that in position 4 as a *para*-compound. Usually these are contracted to *o*-, *m*-, and *p*-, or 1:2-, 1:3- and 1:4-, e.g.¹



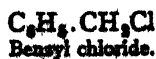
Even when the two substituents are different, three and only three isomerides are known.

The case is otherwise, however, when three hydrogen atoms are replaced by three monovalent elements or radicals. If the substituents are the same, each trisubstitution product can occur in three isomeric forms. These are distinguished from one another as vicinal (1:2:3)-, unsymmetrical (1:2:4)-, and symmetrical (1:3:5)-derivatives of benzene, and are usually written with the corresponding numbers or the abbreviation *v*-, *as*-, or *s*-, before the name of the compound, e.g.,



On the other hand, when the three substituents are not all the same the number of isomerides is greater than three. Should two be identical, as in the case of the compound $C_6H_3Cl(OH)_2$, six isomerides are possible, and if each of the three substituent groups is different, as in the compound $C_6H_3Cl(OH)CH_3$, theory predicts the existence of twelve isomerides.

Aliphatic radicals such as $-CH_3$, $-C_2H_5$, or $-CH:CH_2$ attached to the benzene molecule are known as *side chains*, and the rest of the molecule is termed the *nucleus* or benzene nucleus. Derivatives of this type possess the character of both aromatic and aliphatic compounds, and on further substitution may yield isomerides of quite different properties, depending on whether the substituent enters the nucleus or side chain, e.g.,

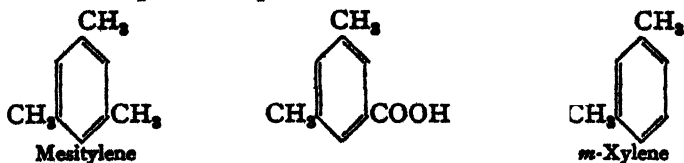


¹ To simplify the formulae and enable the relative positions of substituents to be clearly indicated, the benzene nucleus is commonly represented by a simple hexagon.

Orientation of Polysubstituted Benzene Derivatives

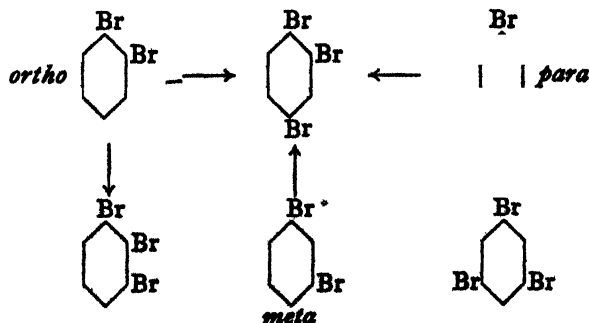
It is obviously of importance to have reliable methods to decide whether a disubstituted benzene derivative is an *ortho*, *meta*, or *para* compound. There are three methods for doing this: (1) by reference to substances of known constitution; (2) by reference to trisubstituted benzene derivatives; and (3) synthesis. Examples will make the value of the methods clear.

(1) Orientation of the three xylenes. Of the three dimethylbenzenes (xylenes) only one on oxidation gives a dicarboxylic acid which forms a cyclic anhydride. The acid can only be phthalic acid and the xylene which yields it must be the *ortho*-compound. The *meta*-compound is obtained from mesitylene 1:3:5-trimethylbenzene, whose structure follows from its synthesis. Partial oxidation of mesitylene gives 3:5-dimethylbenzoic acid which is decarboxylated to *m*-xylene. The third isomer must be the *para*-compound.



Care, however, must be taken in converting substances into compounds of known structure since molecular rearrangements may occur. For example *p*-bromonitrobenzene when heated with potassium cyanide and ethanol at 150° yields a *meta*-product, *m*-bromobenzonitrile.¹ The second method detailed below is free from such objections.

(2) *Körner's method of orientation*. This method was discovered independently by Körner, Griess, and Salkowsky, in 1874. It is based on the fact that each of the isomers $C_6H_4X_2$ gives rise to a different number of trisubstituted derivatives, the *ortho* giving two, the *meta* three, and the *para* one. This is exemplified by the conversion of dibromobenzenes into tribromobenzenes.



(3) An example of the use of synthesis in structural assignment is found in the condensation of acetone to mesitylene (p. 450).

¹ J. F. Burnett, *J. Org. Chem.*, 1950, 15, 481.

Directive Influence of Substituents in the Benzene Nucleus

(1) The nature of a substituent already present in the benzene ring exerts a decisive influence on the position taken up by a second entrant. It is found that a close relationship exists between the *ortho*- and *para*-positions which distinguishes them sharply from the *meta*-position. The hydroxyl group (OH), amino group (NH₂) and alkyl groups, for example, direct a newly entering element or radical predominately to the *o*- and *p*-positions, whereas a group such as NO₂ or SO₃H directs mainly to the *m*-position. (2) In general, *o*, *p*-directive groups facilitate further substitution, whilst those of *m*-directive type increase its difficulty.

A systematic comparison of the directive powers of different groups was begun in 1895 by Holleman,¹ who measured the velocity of various reactions under standard conditions. Nitrations, for example, were conducted at 0° with fuming nitric acid. The relative directive powers of two groups were determined by introducing a third substituent into a benzene ring in which the two groups were already present, followed by a quantitative analysis of the resulting mixture. For the latter purpose, new methods of estimation had to be devised, one of the most useful being by means of fusion curves. Thus *p*-chlorotoluene on nitration gave a product containing more of the isomeride in which a nitro group is *ortho* to chlorine than of that having the nitro group *ortho* to methyl. Chlorine was therefore concluded to have a stronger directive power than methyl. One of the most interesting points which emerged from this work was that in the majority of cases where a monosubstituted benzene is further substituted, the reaction leads to a mixture of *o*-, *m*- and *p*-derivatives, although generally in very unequal proportions.

Holleman found that *m*-directing groups were more weakly directing than the *op*-directive groups, and expressed some of his conclusions as follows :

op-Substitution, proceeds rapidly.



m-Substitution, proceeds slowly.



Many attempts have been made to classify elements and radicals according to their directive influence, some of the more useful of which may be mentioned briefly.

The *Crum Brown and Gibson rule*² states that if the radical already present (CHO, COOH, NO₂, SO₃H) forms a compound with hydrogen which can readily be converted by direct oxidation into the corresponding hydroxyl compound, the second substituent will enter the *meta*-position. Otherwise it will assume the *ortho*- and *para*-positions.

¹ Compare Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (Veit & Co., Leipzig, 1910). Reese, *Chem. Rev.*, 1934, 55.

² *J.*, 1892, 61, 367.

Vorländer's rule divides substituents into unsaturated groups (NO_2 , CN , COOH and SO_3H) causing *m*-substitution, and saturated substituents (Cl , Br , OH , CH_3) leading to *o*- and *p*-substitution.

Unfortunately, although these rules apply to the majority of the simpler cases, they are subject to exceptions and on occasion are mutually contradictory. Cinnamic acid, for example, with the acidic unsaturated substituent $-\text{CH}=\text{CH}-\text{COOH}$, nitrates in the ortho- and para-positions. Moreover, the normal directive influence of COOH or NH_2 may be largely reversed by ionisation. Sodium benzoate in an aqueous solution is chlorinated in the *o*- and *p*-positions; and aniline in the presence of a large excess of sulphuric acid is nitrated mainly in the *m*-position.

Two other rules of orientation which have been advanced recently appear to be of general application. *Hammick* and *Illingworth*¹ have pointed out that in a compound $\text{C}_6\text{H}_5\text{XY}$, when Y is in a higher periodic group than X, or if being in the same group it is of lower atomic weight, then XY is *m*-directive. In other cases, including those in which the substituent is represented by a single atom ($\text{C}_6\text{H}_5\text{X}$), *op*-substitution follows.

Sutton has shown² that the directive influence of the substituent group X is related to the sign of the difference between the dipole moment of the aromatic compound Aryl X and that of the aliphatic analogue Alkyl X. If the expression $(\mu_{\text{Aryl X}} - \mu_{\text{Alkyl X}})$ is positive in value then X is *op*-directive; if the expression is negative then X is *m*-directive. All values of μ are determined for benzene solutions, and where possible comparable data are employed by using those for aliphatic compounds in which X is linked to a tertiary carbon atom. Some of these values are given in the following table.

X.	$\mu_{\text{Aryl X.}}$	$\mu_{\text{Alkyl X.}}$	Diff.	Directive Effect
CH_3	+0.41	0	+0.41	<i>op</i>
Cl	-1.56	-2.15	+0.59	<i>op</i>
Br	-1.53	-2.21	+0.68	<i>op</i>
I	-1.30	-2.13	+0.83	<i>op</i>
CH_2Cl	-1.82	-2.14	+0.32	<i>op</i>
CCl_3	-2.07	-1.57	-0.50	<i>m</i>
CN	-3.90	-3.46	-0.44	<i>m</i>
NO_2	-3.97	-3.29	-0.68	<i>m</i>

Additional confirmation of Sutton's work is provided by the data of Groves and Sugden relating to measurements in the vapour state.³

The differences are mainly due to the high polarisability of the benzene nucleus. They show that where the group X is *op*-directive there is an electron displacement from the substituent towards the ring; this permanent effect is therefore in the direction which facilitates *op*-substitution. With *m*-directive groups the displacement is in the opposite sense and assists *m*-substitution (compare electronic theory of benzene substitution).

¹ *J.*, 1930, 2352.

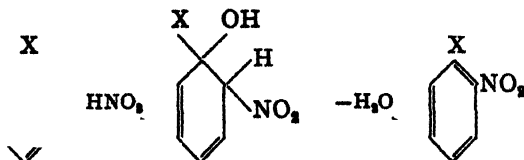
² *Proc. Roy. Soc.*, 1931, 133 A, 668.

³ *J.*, 1935, 973.

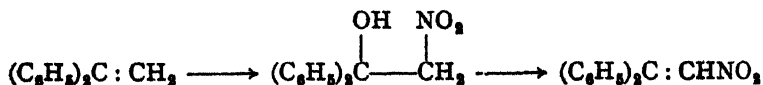
Electronic Theories of Benzene Substitution HETEROLYTIC SUBSTITUTION

Aromatic compounds undergo substitution either by ionic (*heterolytic*) attack or by free radical (*homolytic*) attack, and we shall consider these two types of reaction separately.

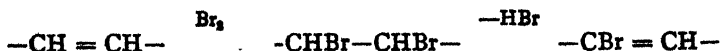
The mechanism of aromatic substitution has attracted many investigators, and of the theories advanced that of Holleman gained wide acceptance. According to this theory aromatic substitution is fundamentally an addition of the reagent at a nuclear double bond followed by the loss of water to give the final product.



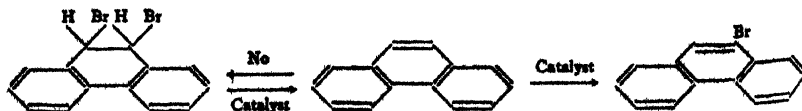
The scanty experimental support for Holleman's theory has been reduced by later investigations. Wieland, for instance, succeeded in isolating addition compounds during the nitration of olefin derivatives, e.g.¹



Michael showed,² however, that such compounds are due to oxidation and not to nitration. A still more instructive example is provided by the bromination of phenanthrene. The 9:10-dibromide is first formed and, on further heating, 9-bromophenanthrene is obtained. The most obvious mechanism is addition of bromine at the double bond followed by elimination of hydrogen bromide.



This was shown by Price³ to be incorrect since 9:10-phenanthrene dibromide is not an intermediate in the formation of 9-bromophenanthrene. Bromine may react with phenanthrene in two distinct ways. In non-aqueous solvents without a catalyst the dibromide is formed, while in presence of a halogen-carrier such as iodine 9-bromophenanthrene is obtained. Further, the addition reaction is reversible while the substitution is not.



¹ Wieland and co-workers, *Ber.*, 1920, 53, 201; 1921, 54, 1770. Barnett and Cook, *J.*, 1924, 205, 1064. Fries and Engel, *Ann.*, 1924, 439, 232. ² A. Michael and G. H. Carlson, *J.A.C.S.*, 1935, 57, 1268. ³ Price, *J.A.C.S.*, 1936, 58, 1834, 2101.

In presence of a suitable catalyst the dibromide is converted into 9-bromophenanthrene, but only because it reverts to phenanthrene which then undergoes substitution. Here then we have a case of an addition product which is not an intermediate in the substitution reaction. The present view is that the majority of substitutions of aromatic compounds occur by direct attack of the reagent at a CH-group, and involve simultaneous addition of the entering group and removal of hydrogen.

Over a period of years important theories of benzene substitution were advanced by Flürscheim, Lapworth and Fry, and these have contributed to the present point of view as represented in the electronic theories elaborated by Robinson¹ and Ingold.² In giving a brief outline of this final development, a resumé may also be made of the main experimental facts on which it is based and of the typically aromatic reactions it attempts to explain.

As already noted the most striking characteristics of aromatic chemistry are the predominantly *op*- or *m*-directive influence of groups attached to the nucleus and the rapidity of the former type of substitution as compared with the latter, a peculiarity which was first emphasised by Holleman. Additional information on this point has been provided by Wibaut and by Ingold, who showed that toluene is nitrated fourteen times as fast as benzene, thus proving that even the methyl group strongly facilitates substitution in the ring. On the other hand, halogenated benzenes are exceptional in being attacked more slowly than benzene itself, although they also yield *o*- and *p*-derivatives.

The most powerful directive influence of all is exerted by a substituent bearing an integral charge such as the ionised hydroxyl group (\bar{O}) of phenoxides,³ which are brominated with great velocity and almost entirely in the *o*- and *p*-positions, and the NMe_3^+ group of phenyltrimethylammonium salts which slowly yield a pure *m*-derivative. The remarkable influence of this last group is illustrated in the following percentages of *m*-compound formed,⁴ corresponding data for the strongly *m*-directive nitro group being also given.

$C_6H_5.NMe_3$ 100	$C_6H_5.CH_2.NMe_3$ 88	$C_6H_5.CH_2.CH_2.NMe_3$ 19
$C_6H_5.NO_2$ 93	$C_6H_5.CH_2.NO_2$ 48	$C_6H_5.CH_2.CH_2.NO_2$ 13

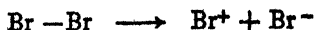
Even when separated from the nucleus by two carbon atoms, the trimethylammonium group gives rise to no less than 19 per cent. of *m*-derivative.

Comparisons of the above nature inevitably led to the conclusion that the aromatic nucleus is activated by negatively charged substituents and

¹ Robinson, *Outline of an Electrochemical Theory of the Course of Organic Reactions* (Institute of Chemistry, 1932). ² Ingold, *Chem. Rev.*, 1934, 15, 225. ³ See Soper and Smith, *J.*, 1926, 1582; 1927, 2757. ⁴ Ingold, *Rec. trav. chim.*, 1929, 48, 805. For similar effects in oxonium and quinolinium salts see R. J. W. Le Fèvre and co-workers, *J.*, 1929, 2771; 1930, 2235.

AROMATIC COMPOUNDS

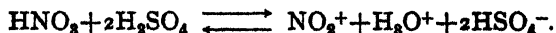
deactivated by those carrying a positive charge. They also confirmed the belief that the attacking reagent is *electrophilic (cationoid)* in character, seeking a point in the molecule at which there is a high electron density. In bromination, for example, one bromine atom appears in the final mixture as bromide ion; the effective agent is thus positively charged bromine liberated by the unsymmetrical disruption of molecular bromine.



Similarly, nitric acid reacts in the form $\text{HO}\cdot\text{NO}_2$, the hydroxyl taking with it on separation both of the covalency electrons originally binding it to nitrogen and leaving the positive residue $+\text{NO}_2$ to attach itself to the nucleus at a point where the nitrogen octet may be completed.

Experimental confirmation that aromatic substitution (nitration, halogenation, etc.) is effected by positive ion (electrophilic) attack recently been provided.¹ C. K. Ingold and E. D. Hughes, G. M. Ben and G. Williams in England; J. Chedin in France; and F. H. Weston and M. S. Kharasch in the United States have demonstrated by physical methods that in mixed acid, *i.e.* concentrated sulphuric and nitric acids the positive nitronium ion, NO_2^+ , is present and it is this ion which is the nitrating agent. The evidence is based upon cryoscopic, vapour pressure, electrical conductivity, and spectroscopic data.

Cryoscopic Evidence. Freezing-point depression measurements of nitric acid in sulphuric acid requires a van't Hoff factor of 4. This is in agreement with the formation of nitronium ion according to the equation:



Vapour-pressure Evidence.—The partial vapour of nitric acid is reduced by the addition of sulphuric acid until finally it is reduced to nothing. This is simply and reasonably accounted for by the conversion of the nitric acid into the non-volatile nitronium and hydroxonium ions.

Electrical Conductivity.—Solutions of nitric acid in sulphuric acid have a high conductivity. The former acid contains a cation since it migrates to the cathode. This ion is the nitronium ion, whose existence is confirmed by the isolation of solid nitronium salts $(\text{NO}_2^+)(\text{HSO}_4^-)$ and $(\text{NO}_2^+)(\text{ClO}_4^-)$.

Spectroscopic Evidence.—In water nitrates and nitric acid show an absorption band at *ca.* $300\text{ m}\mu$ which is characteristic of the nitrate ion. If water is gradually replaced by sulphuric acid this band is gradually replaced by another at $270\text{ m}\mu$. This change is attributed to nitronium ion formation. Additional evidence has been afforded by Raman spectra. The nitronium ion is isoelectronic with carbon dioxide, and would therefore be expected to have a linear structure and give rise to a depolarised Raman line near 1400 cm^{-1} . Solutions of nitric acid in sulphuric

¹ For surveys of the evidence see E. A. Braude, *Ann. Reports*, 1949, 46, 131. M. J. S. Dewar, *ibid.*, 1951, 48, 128.

acid do in fact exhibit not only a line at 1030 cm.⁻¹ (nitrate ion), but also one at 1400 cm.⁻¹ (nitronium ion).

The electrophilic character of aromatic halogenation has also been confirmed experimentally.¹ Hypobromous acid does not react with benzene in dilute aqueous solution, but on the addition of mineral acid it acts as a brominating agent. This is readily accounted for by the postulate that hydrogen ion and hypobromous acid generate positive bromine ions (Br^+ or H_2OBr^+).



Detailed investigation has shown that positive bromine ions are indeed formed and act as brominating agents.

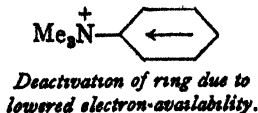
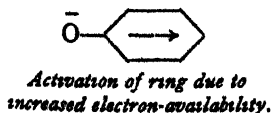
In an extension of their work, Derbyshire and Waters² have developed a method for bromination, not with free hypobromous acid which requires careful preparation, but with acidified bromine water in the presence of silver or mercuric salts.



The bromine anions are removed by the silver or mercuric ions and the remaining hypobromous acid then generates bromine cations as shown above. In this way chlorobenzene, bromobenzene, benzoic acid, etc. give good yields of the expected bromo-products. Substances such as *m*-dinitrobenzene which are not smoothly brominated by the usual methods even at 100° give good clean products by the new method. This incidentally emphasises the efficiency of the bromine cation as a brominating agent.

Similar evidence has been presented in favour of chlorination and iodination by chlorine and iodine cations respectively.³

According to the electronic theories of Robinson and Ingold, one way in which the influence of a negatively or positively charged substituent is passed on to the ring is by the **inductive effect** (see p. 74). A negatively charged group will repel the covalency electrons in the nucleus and so render them more readily available to a suitable reagent; a positively charged group will attract the electrons and thus reduce the reactivity of the ring. These conditions are represented diagrammatically as follows.



Less powerful influences of the same kind are assumed to arise from the dipoles of polar groups, whether electropositive (CH_3 , NH_2) as in II, or electronegative (NO_2 , COOH , SO_3H) as in IV. In these cases the

¹ D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 1950, 564.
² *Ibid.*, 1950, 3694; 1951, 73.

³ *Ibid.*, 1950, 573.

effect is caused by one pole of the dipole being nearer the ring than the other, and the inductive influences are naturally weaker than those due to an ionic group. Ingold describes the change in the nucleus indicated in I and II as a $+I$ effect, and the reverse change shown in III and IV as a $-I$ effect.



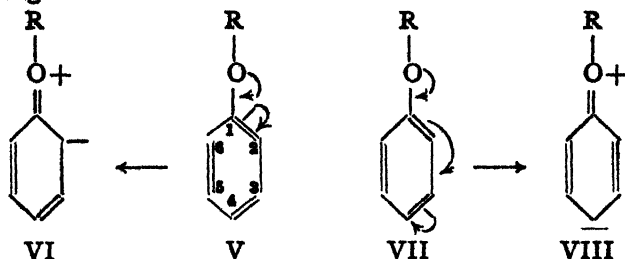
The characteristic properties of aromatic compounds, however, cannot be adequately interpreted in terms of the inductive effect alone. No explanation is provided for the alternation of reactive and non-reactive points in the aromatic ring, nor for the fact that the speed of substitution by electrophilic agents is not reduced by *all* electronegative groups. Some substituents, notably hydroxy and alkoxyl, resemble the electropositive methyl, amino and alkylamino groups in leading to a greatly increased rate of attack.

A similar difficulty arises in tracing the effect of a substituent on acidic strength. Nathan and Watson showed that the dipole moment of a group X present in an aliphatic acid, $X \cdot CH_2 \cdot COOH$, may be directly correlated with the dissociation constant of the acid. But this simple relationship does not hold for aromatic acids. A methoxyl group increases the dissociation constant of acetic acid and also of benzoic acid when present in the *m*-position, whereas the same group in the *p*-position considerably lowers the strength of benzoic acid. On the other hand, a nitro group in the *p*-position raises the dissociation constant of benzoic acid more than one in the *m*-position, despite its greater proximity to the carboxyl group in the latter case. Halogens exert a greater influence in the *m*- than in the *p*-position, but their relative effects among themselves are not the same as those found in the acetic acid series.

It thus became clear that an electrical effect of another type is being relayed from the substituent group, and one which may on occasion act in opposition to the induced effect. This second factor, known as the **tautomeric effect**, is based on Lowry's idea of *electromeric change* (see p. 77) and the modern conception of mesomerism. A clue to its nature was given by the observation that abnormal results follow the introduction of groups having unshared electrons on the atom linked to the nucleus. Such an atom has the possibility of transferring a pair of electrons by electromeric change so as to form a double bond between it and the adjoining carbon atom. By further electromeric rearrangement an ortho- or para-quinonoid structure may be formed. This transformation is readily visualised in the case of hydroxy and amino derivatives, since quinones and quinonimines represent well-known structures.

In an alkoxy benzene the process may be formulated provisionally in

the following way. On the completion of the double bond between O and C_1 (see fig. V), the valency sheath of the latter is reduced to eight again by the release of two electrons from the double bond C_1C_2 , converting this into a single bond.



The released electrons may then remain in the unshared state on C_2 , yielding the *o*-quinonoid form VI, which will undergo substitution most readily in the negatively charged *o*-position. Alternatively, the charge may be passed on directly from C_1C_2 to C_3C_4 (see fig. VII), transforming the single into a double bond, followed by the withdrawal of two electrons of the C_5C_6 double bond to C_4 , in order to bring the number at the *m*-position down to eight. The negative charge in the resulting *p*-quinonoid structure VIII is at C_4 , leading to substitution at this point. Without violation of the octet rule the charge cannot be represented as remaining at the *m*-position, hence activation occurs at the *o*- and *p*-positions.

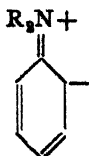
The theory, however, regards the alkoxy benzene as existing in a definite state of mesomerism, with each of the forms V, VI and VIII, as well as the corresponding arrangements derived from the other Kekulé form having double bonds at 2 : 3, 4 : 5 and 1 : 6, making its contribution to the actual resonance structure. The latter is therefore more correctly formulated with small negative charges (δ^-) at the *o*- and *p*-positions, which arise as indicated from the *incomplete* electron displacements. The assumption of a permanent polarisation of this kind is supported by Sutton's generalisation on dipole moments of aliphatic and aromatic compounds of the type RX already discussed on p. 437. Ingold describes it as the **mesomeric effect**, M , prefixed in the case under consideration by a positive sign ($+M$). At the demand of a suitable reagent, situated in proximity to an activated position, reaction ensues leading to the *completed* electromeric change ($+E$) shown in the above mechanism. The tautomeric effect is therefore made up of the two effects respectively described as mesomeric and electromeric, $T = M + E$.

The final stages of reaction may be illustrated in the case of bromination. After Br^+ has attached itself to the negatively charged carbon atom ($>CH^-$) to form the neutral group $>CHBr$, the proton is assumed to become detached, leaving carbon once again with a negative charge as $>CBr^-$. By a reversal of the electromeric changes already depicted, the positive and negative charges are neutralised, leaving the ring in the normal aromatic state ($>CBr$).

Amino-compounds and their alkyl derivatives may give rise to a tautomeric effect similar to that of hydroxy and alkoxy compounds leading to contributing structures of the types IX, X and XI.



IX

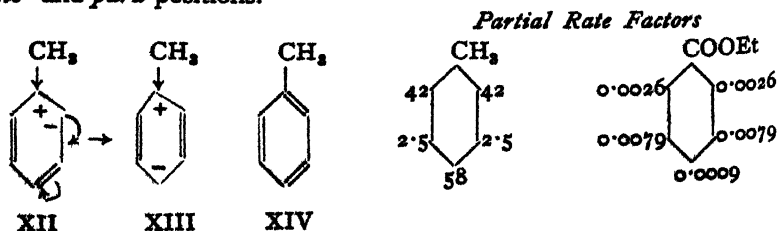


X



XI

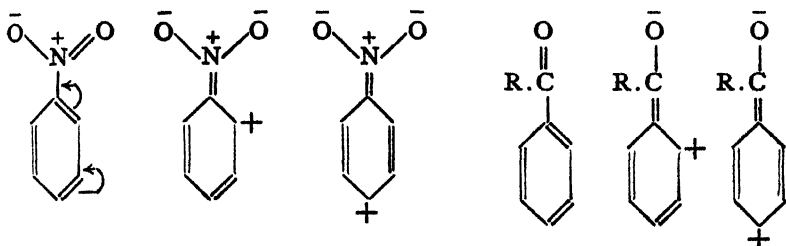
Among the remaining types of *op*-directive substituents, halogens and alkyl groups have also been investigated, but here the mechanism by which the influence is transmitted is not so clearly established.¹ It is probable that with halogens the same inductive and tautomeric effects operate as have been postulated in the case of alkoxy compounds, even though the corresponding quinonoid forms resulting from increased covalence of halogen with the ring have not actually been isolated. With alkyl benzenes there is no possibility of a tautomeric effect, since there are no unshared electrons on the carbon atom of the alkyl group attached to the nucleus. A methyl group, however, exerts a definite if small electron-repulsion, as shown by its influence in weakly depressing the acidic strength of an aliphatic acid and by the small positive dipole moment of toluene. The directive power of the group is therefore believed to be due to an inductive effect, which leads primarily to the polarisation of the adjacent double bond, C₁C₂, so that on activation the negative pole is developed in the ortho position (XII). By electromeric change the structure XII may be transformed into XIII. These two types may thus be regarded, together with XIV, as contributing to the mesomeric state. The general inductive effect (+I) means that there will be an increased electron-availability at *all* points in the ring. This has been proved by the competitive nitration of a mixture of toluene and benzene.² From the data thus obtained Ingold calculated the *partial rate factors*, which give the rate of substitution of the individual positions in the toluene ring, the rate of substitution for any position in the benzene ring being taken as unity. From the figures shown below it is seen that the methyl group activates all positions in the ring and particularly the *ortho*- and *para*-positions.



¹ For a discussion of these cases see Ingold, *Chem. Rev.*, 1934, 25, 238; H. B. Watson, *Modern Theories of Organic Chemistry* (Oxford, 1941), p. 101.
² Ingold, Lapworth, Rothstein and Ward, *J.*, 1934, 1939.

support for the above interpretation is also found in the dissociation constants of the toluic acids, the value for the *p*-compound being somewhat less than that for the *m*-derivative.¹

m-Directive groups also have no unshared electrons on the atom linked to the ring. All such substituents are strongly electronegative and are represented as giving rise to electromeric displacements in the opposite direction to those developed in alkyl or alkoxy derivatives. A typical case is that of a nitro-compound, for which the forms contributing to the resonance structure are shown below. In the normal state, therefore, the compound may be regarded as having fractional positive charges at the *o*- and *p*-positions. Owing to the inductive effect ($-I$), the electron-

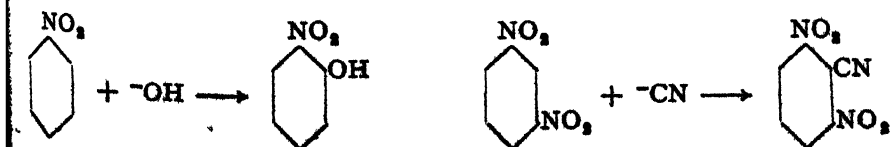


availability is diminished over the *whole* nucleus, while the mesomeric effect ($-M$) results in deactivation being particularly evident in the *o*- and *p*-positions. Hence substitution proceeds comparatively slowly and at the *m*-position.

Here again these speculations have been confirmed by the determination of the partial rate factors for the nitration of ethyl benzoate. The general deactivation particularly at the *ortho*- and *para*-positions is obvious.

A similar state of affairs occurs when the directive substituent is a ketonic group. In all cases the structures derived from the Kekulé form with the double bonds in the alternate positions also contribute to the resonance state.

On the foregoing theory of benzene substitution it is to be expected that the normal directive powers of groups will be reversed when the reagent is **nucleophilic** instead of electrophilic in character, *i.e.* one containing an atom with its full complement of electrons and able to play the part of a "donor" towards an "acceptor" with an incomplete sheath. Reactions of this kind are already well known. Thus nitrobenzene heated with strong potassium hydroxide yields *o*-nitrophenol,



¹ Dippy and Lewis, *J.*, 1936, 644.

and *m*-dinitrobenzene reacts with potassium cyanide to give 2 : 6-dinitrobenzonitrile. The nuclear hydrogen is eliminated during these changes in the form of potassium hydride. Another example of the same is the interaction of pyridine with sodamide (NH_2^-) to produce 2-aminopyridine.

It is obvious from the foregoing pages that in a highly speculative field such as this direct experimental verification is very desirable. This has in recent years been provided by Ingold's work referred to p. 444; by the researches in several laboratories on the mechanism of nitration (p. 440); and by infra-red absorption studies of certain phenols.

As a result of the tautomeric effect the oxygen-carbon bond in phenol is endowed, to a certain extent, with double-bond properties and as a consequence *cis-trans* isomerism should be detectable in *o*-substituted phenols such as *o*-chlorophenol.



This has been done by measurement of the infra-red absorption of *ortho*-substituted chlorophenols. Phenol has a 7050 cm^{-1} band characteristic of the "free" phenolic group, while the single band of 2 : 4 : 6-trichlorophenol at 6900 cm^{-1} is attributed to the chelate structure exemplified in the above *cis*-form. *o*-Chlorophenol shows both bands, the latter much more intensely than the former, and from this it is concluded that the carbon-oxygen link has double-bond properties giving rise to *cis*- and *trans*-isomers with the former predominating.

Homolytic Substitution of Aromatic Compounds¹

The so-called aromatic reactions—nitration, sulphonation, etc.—are undoubtedly ionic reactions and are electrophilic. It was shown in the foregoing discussion that substituents in the benzene ring influence electrophilic substitution in a well-defined manner, and as a result substituents are divided into two categories according as they are *ortho*-, *para*- or *meta*-directing. The former substituents generally facilitate further substitution in the ring, while the latter invariably retard it.

This characteristic specificity is entirely lacking when benzene derivatives are attacked by free radicals, *i.e.* when they undergo *homolytic substitution*. This is at once obvious from the data given in the following table in which the results of free-radical phenylation and hydroxylation on benzoic acid, nitrobenzene, and chlorobenzene are given.

¹ D. H. Hey, Tilden Lecture, *J.*, 1952, 1974. W. A. Waters, *Ann. Reports*, 1952, 49, 121.

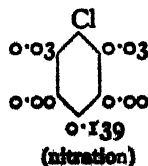
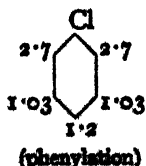
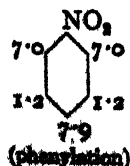
Homolytic Substitution

Substance.	Process.	Per cent. Yield of Isomerides.			Ref.
		<i>ortho</i> .	<i>meta</i> .	<i>para</i> .	
Benzoic acid . .	Hydroxylation (Ionising radiation)	30	20	50	1
Nitrobenzene . .	Hydroxylation (Fenton's Reagent)	25-30	20-25	50-55	2
	Hydroxylation (Ionising radiation)	35.5	29	35.5	
Chlorobenzene . .	Phenylation	58	10	32	3
	Hydroxylation (Fenton's Reagent)	40-45	20-25	20-25	4
	Hydroxylation (Ionising radiation)	15-20	20-25	50-60	4
	Phenylation	62	24	14	5

- ¹ J. Weiss and G. Stein, *J.*, 1949, 3245. H. Loebl, G. Stein and J. Weiss, *J.*, 1951, 405.
² H. Loebl, G. Stein and J. Weiss, *J.*, 1949, 2074; 1950, 2704. ³ D. R. Augood, D. H. Hey
and G. H. Williams, *J.*, 1952, 2095. ⁴ G. R. A. Johnson, G. Stein and J. Weiss, *J.*, 1951, 3275.
⁵ D. R. Augood, D. H. Hey and G. H. Williams, *J.*, 1953, 44.

These results differ fundamentally from those of heterolytic substitution and show that homolytic attack is not subject to the usual directive influence of substituents. Nitrobenzene, for instance, affords about 60 per cent. of the *ortho*-product on phenylation and only about 10 per cent. of the *meta*, in strong contrast to its formation of *m*-dinitrobenzene on nitration. Chlorobenzene likewise gives about a 60 per cent. yield of *ortho*-product on phenylation, but here the yield of *meta*-product is greater than that of *para*.

The difference between electrophilic and homolytic attack is further demonstrated by competitive experiments which show, for example, that nitrobenzene is phenylated four times as fast as benzene. The nitro group therefore has a deactivating influence on electrophilic attack but an activating effect on homolytic attack. This behaviour is shown even more clearly by the partial rate factors (p. 444), which measure the rate of substitution in the *o*-, *m*-, and *p*-positions of a molecule C_6H_5R compared to the rate of substitution at any one carbon atom in benzene. In the following diagrams the partial rate factors for the phenylation of nitrobenzene and chlorobenzene as well as those for the nitration of chlorobenzene (nitric and acetic acids) are shown.

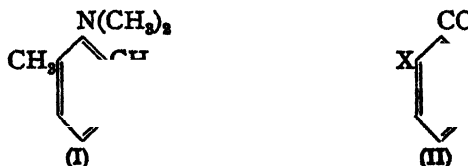
Partial Rate Factors

From these figures it is clear that the nitro and chloro groups activate all groups in homolytic reactions, whereas the chloro group deactivates all positions towards electrophilic attack.

Summarising, it can be said that homolytic substitution does not obey the "aromatic substitution laws". This difference has been attributed to the fact that an attacking ion perturbs the aromatic molecule and converts it by a tautomeric change into quite a different state from the mesomeric stable state. Homolytic substitution, on the other hand, is non-polar and free radicals consequently attack the unperturbed molecule.¹

Steric Hindrance²

Ortho substituents in contrast to substituents in the *meta* and *para* positions often exert a striking interference in hindering or completely preventing the progress of reactions which otherwise proceed with ease. Dimethylaniline behaves as a typical tertiary amine and readily forms a quaternary ammonium salt with methyl iodide; but if two methyl groups are inserted in the two *ortho*-positions, the resulting compound (I) forms no quaternary ammonium salt. To account for this and other similar



observations, F. Kehrman postulated that the responsible factor is the volume or bulk of the substituents, which in consequence inhibit or hinder chemical reaction at the reaction centre. In other words it is a blocking effect caused by the geometry of the molecule. Kehrman also studied the influence of size of the blocking groups and showed, for instance, that the isopropyl group as would be expected has a much greater impeding effect than the smaller methyl group. Subsequently it was shown that many other reactions are subject to the impeding effect of *ortho*-substituents. Specially calling for mention are the researches of Victor Meyer on the esterification of acids by alcohols and hydrogen chloride. Meyer found that whenever the two hydrogen atoms in the *ortho*-positions to the carboxyl group of benzoic acid are replaced by atoms or radicals such as Cl, Br, CH₃, NO₂, or COOH, the resulting acid (formula II) cannot be thus esterified. Similarly if an acid of this type is once converted into an ester by other means (*e.g.* by the use of the silver salt and ethyl iodide) the ester is very difficult to hydrolyse. Meyer, like Kehrman, ascribed the effect to mechanical blocking of the reactive centre by the *ortho*-substituents, and coined the expression *steric hindrance* to denote the phenomenon.

¹ W. A. Waters, *Trans. Far. Soc.*, 1941, 37, 772. ² For a full discussion of steric hindrance see E. D. Hughes, *Quart. Reviews*, 1948, 22, 107.

There is no doubt that *ortho*-substituents frequently exert a blocking effect (see, for instance, diphenyl isomerism, p. 38), but closer analysis has shown that other factors such as the mechanism of the reaction and the polarity of the substituents must also be taken into consideration. It is known, for example, that sterically hindered acids may be esterified by the interaction of their silver salts with methyl iodide. The Fischer-Speier method probably fails because it involves an attack on the carbon atom of the carboxyl group, whereas in the silver salt method reaction occurs at an oxygen atom of the carboxyl group. In other words reaction occurs readily at the oxygen atom because it is more remote from the benzene ring. It must also be noted that *ortho*-substituents may accelerate the rate of a reaction. A good example of this is the mobility of the chlorine atom in *o*-chloronitrobenzene which stands in sharp contrast to the inertness of the chlorine in chlorobenzene (see p. 459). Here the polar properties of the nitro-group overcome its steric effect.

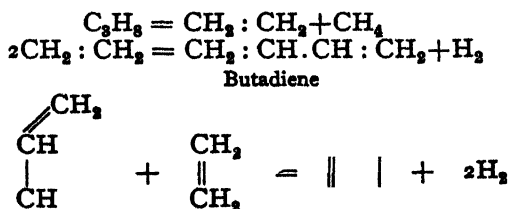
Chelation (p. 90) is another effect which is occasioned by the proximity of groups in *ortho*-substituted compounds.

It must be concluded that substituents in the *ortho*-position exert an influence on one another which is not observed in the isomeric *m*- and *p*-derivatives and thereby gives rise to what is commonly described as the "*ortho*-effect." This effect, as we have seen, may be either geometrical or polar in origin.

Formation of Cyclic from Open-chain Compounds

Aliphatic compounds may be transformed into those of the aromatic series in a number of ways, one of which is of historical interest and has already been referred to on p. 274. A few of the more important methods are given below.

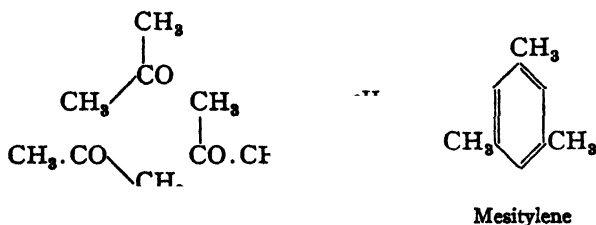
1. Paraffins and unsaturated aliphatic hydrocarbons when submitted to a high temperature (*pyrolysis*) polymerise to aromatic products. The paraffins probably yield aromatic hydrocarbons through intermediate unsaturated hydrocarbons. The conversion of propane into benzene occurs by a degradation to ethylene. This then is partly condensed to butadiene. Finally the ethylene and butadiene react to give benzene and hydrogen.



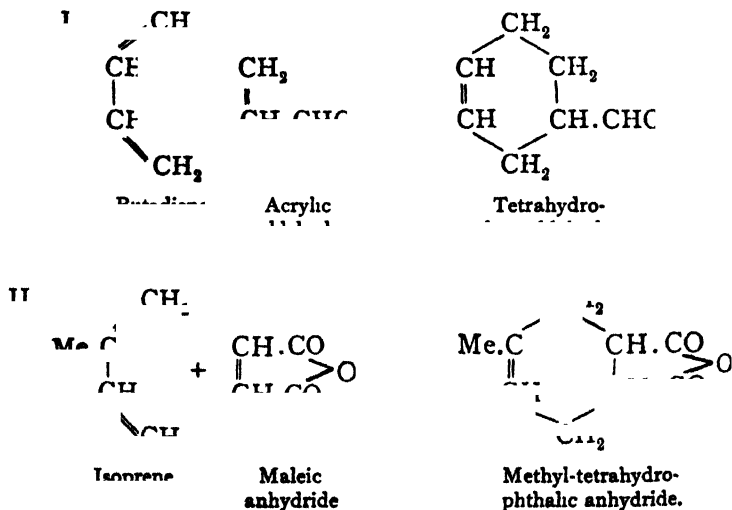
Berthelot in his classic researches on pyrolysis found that acetylene at 500° yields benzene, $3\text{C}_2\text{H}_2 = \text{C}_6\text{H}_6$. In recent years with the aid

of catalysts such polymerisations can be effected under very mild conditions. For instance, acetylene at 60-70° and 15 atmospheres pressure with a nickel carbonyl catalyst gives an 88 per cent. yield of benzene and 12 per cent. of styrene.¹

A very useful method for preparing aromatic hydrocarbons is found in the self-condensation of aldehydes and ketones. One of the earliest examples of this is the condensation of acetone by means of sulphuric acid to give mesitylene, 1 : 3 : 5-trimethylbenzene (R. Kane, 1838).

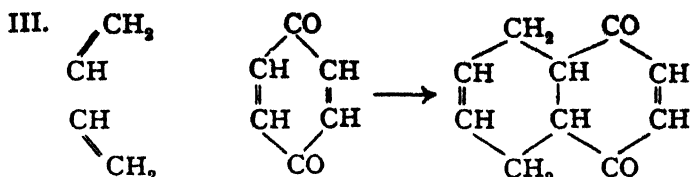


(2) *Diels-Alder Reaction*.² Butadiene and ethylene (a *dienophile*) react at 200° and high pressure to give *cyclo*-hexene. Otto Diels and Kurt Alder, however, showed that, if the dienophile contains an activating group such as the carbonyl group, reaction occurs smoothly under very mild conditions. Typical dienophiles are maleic anhydride, acrylic aldehyde, and *p*-benzoquinone. The products are partially hydrogenated aromatic compounds and three typical examples of the reaction are given below.



¹ W. Reppe and W. J. Schweckendick, *Annalen*, 1948, 560, 104.
² For reviews of the reaction, see J. A. Norton, *Chem. Reviews*, 1942, 31, 319. M. C. Kloetzel and H. L. Holmes *Organic Reactions* (Editor, Roger Adams), vol. 4, pp. 1-60.

² For reviews of the reaction, see J. A. Norton, *Chem. Reviews*, 1942, 31, 319. M. C. Kloetzel and H. L. Holmes *Organic Reactions* (Editor, Roger Adams), vol. 4, pp. 1-60.



Instead of butadiene a variety of cyclic unsaturated hydrocarbons may be used.

The characteristics of the reaction are the low temperatures required, the absence for the most part of side-reactions, and the fact that catalysts are not required. From consideration of the examples given above it is clear that ring-closure occurs by 1 : 4-addition of the dienophile on the diene. The reaction is one of the most versatile in organic chemistry and has been used to synthesise thousands of compounds, many of which cannot readily be prepared by any other method. For their discovery of the reaction Diels and Alder in 1950 were jointly awarded the Nobel Prize for Chemistry.

3. Alicyclic compounds can be dehydrogenated by a variety of methods to aromatic compounds. Thus the partially hydrogenated aromatic products of the *Diels-Alder* reaction (see above) are readily converted into the corresponding aromatic compounds. In Vesterberg's method the hydroaromatic compound is heated with sulphur. Hydrogen is removed in the form of hydrogen sulphide and an aromatic compound is obtained (see, *e.g.*, p. 413). In recent years this method has been replaced by selenium dehydrogenation (see p. 627). Platinum and palladium are not only efficient hydrogenating catalysts, but are also efficient dehydrogenating catalysts; and, thanks largely to the pioneer work of N. D. Zelinski, they are often used for this purpose. Cyclohexane, for example, when heated to 300° with palladium or platinum is converted into benzene. Examples of these and other dehydrogenating agents will be found in the sequel.

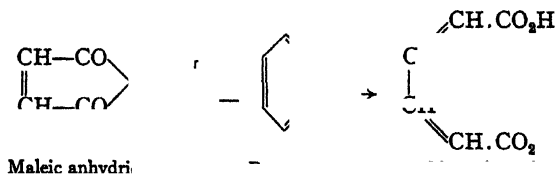
4. Alicyclic compounds are much less stable than the corresponding aromatic isomers, and consequently it is not surprising that by the aid of heat or catalysts they are isomerised to aromatic compounds. The terpene ketone carvone, for instance, is a stable substance which distills unchanged, but when heated at 450° with clay chips it yields the phenol carvacrol. Many other examples of the aromatisation of terpenes and related compounds are known.¹

Rupture of the Benzene Ring

Oxidation is frequently used for fission of the benzene ring. Benzene vapour for instance is catalytically oxidised to maleic anhydride. The

¹ For a review of the subject, see E. C. Horning, *Chem. Rev.*, 1943, 33, 89.

biological oxidation of benzene on the other hand affords muconic acid an acid which is also obtained by the peracetic acid oxidation of pheno



or catechol.¹ The ease with which the last-named substances yield an open-chain compound is illustrative of the fact that the presence of certain groups such as the amino or hydroxyl greatly increases the ease with which the benzene ring is ruptured.

Nevertheless under normal conditions benzene and many substituted benzenes are resistant to most oxidising agents. An exception is ozone, which as already stated (p. 430) attacks benzene and forms a triozone. The triozone on decomposition gives glyoxal.

Certain aromatic substances are reduced by alkaline reagents to open-chain products. The best known example of this method of ring-fission is the reduction of salicylic acid to pimelic acid by sodium and boiling amyl alcohol.

IV

Benzene and its Homologues

Benzene is formed during the dry distillation of coal, and, as already described, is prepared industrially from coal tar or coal gas. Although the percentage of benzene present in petroleum is exceedingly small, recent improved extraction methods have led to the recovery of benzene from this source on the large scale. It was first isolated by Faraday in 1825 from the illuminating gas obtained from oil; it was prepared from benzoic acid by Mitscherlich in 1834, and its presence in coal tar discovered in 1845 by A. W. Hofmann. Pure benzene may be obtained by the decarboxylation of benzoic acid. This is accomplished by distilling sodium benzoate with soda-lime.

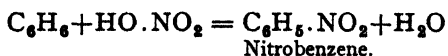


Benzene is a colourless, strongly refracting liquid of peculiar aromatic taste and smell, boiling at 80.4° under 760 mm. and melting at $+5.4^\circ$. It burns with a luminous sooty flame, is insoluble in water, but is miscible in all proportions with alcohol and ether, and forms an excellent solvent for resins, fats and sulphur.

¹ T. A. Elvidge. R. P. Linstead. P. Sims and B. A. Orkin. *J.*, 1950, 2235.

Benzene, the prototype of the aromatic hydrocarbons, is characterised by its stability towards oxidising agents and the readiness with which it undergoes substitution but not addition reactions. In other words, although it is most commonly represented by a formula containing three double bonds it does not behave like a highly unsaturated hydrocarbon. This is clearly shown by considering the properties of benzene and its derivatives which differentiate aromatic from aliphatic compounds. These may be summarised as follows :—

1. A most striking feature is the ease with which hydrogen in an aromatic nucleus may be substituted by halogen, the nitro group ($-\text{NO}_2$), and the sulphonic group ($-\text{SO}_3\text{H}$). As mentioned on p. 104, the normal paraffins are attacked little or not at all by concentrated nitric or sulphuric acid, except at high temperatures, whereas the aromatic hydrocarbons and many benzene derivatives are readily nitrated with concentrated nitric acid, or a mixture of this acid with concentrated sulphuric acid :



With concentrated sulphuric acid alone, aromatic compounds are readily converted into sulphonic acids.



These and other reactions which are discussed in the sequel illustrate the most characteristic feature of benzene chemistry in that it undergoes substitution and not addition reactions.

2. Homologues of benzene, such as $\text{C}_6\text{H}_5.\text{CH}_3$ and $\text{C}_6\text{H}_5.\text{CH}_2.\text{CH}_3$ differ from the paraffins in the ease with which they undergo oxidation ; the latter resist attack, while the former are readily converted into benzene-carboxylic acids such as $\text{C}_6\text{H}_5.\text{COOH}$, the whole of the side chain being oxidised and replaced by a carboxyl group.

3. A striking feature of aromatic halogen compounds as compared with the alkyl halides is the relative inertness of the halogen atom. In chlorobenzene and bromobenzene, for example, the halogen is so firmly united to the nucleus that it can be brought into reaction with ethoxides, ammonia, or amines only with difficulty.

4. Aromatic amines are less basic than aliphatic amines, and the phenols, *e.g.* $\text{C}_6\text{H}_5\text{OH}$, are more strongly acidic than the alcohols. Furthermore the introduction of a phenyl group into the molecule of a carboxylic acid increases the strength of the acid considerably. Thus for $\text{CH}_3.\text{COOH}$, $K \times 10^5 = 1.76$, and for $\text{C}_6\text{H}_5.\text{CH}_2.\text{COOH}$, $K \times 10^5 = 4.88$. The factor responsible for these observations is that the phenyl radical is an intrinsic attractor of electrons.

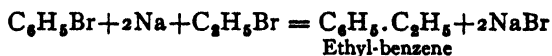
5. Finally, it may be mentioned that aromatic amines react with nitrous acid to give diazonium compounds. These compounds are only rarely found in the aliphatic series.

Preparation of Benzene Homologues

Alkyl derivatives of benzene may be prepared by the condensation of alkyl-acetylenes (see p. 457) and by the following methods:—

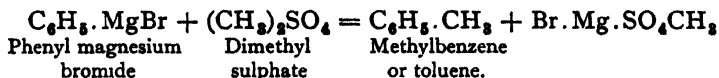
1. By the dry distillation of aromatic carboxylic acids with alkali or soda-lime. In the same manner benzene may be obtained from benzoic acid (see above).

2. By the action of sodium on a mixture of a brominated benzene and an alkyl bromide or iodide, *e.g.*,

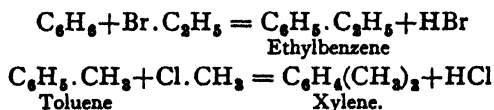


This reaction, discovered by Fittig in 1864, is an extension of the Würtz method of synthesising paraffins by the use of sodium and alkyl halides (p. 108).

3. From aromatic organo-magnesium derivatives by heating with alkyl halides, or more conveniently by the action of alkyl sulphates.



4. The *Friedel-Crafts reaction* is an important method of preparing alkyl-benzenes and aromatic ketones. It consists in bringing aromatic hydrocarbons into reaction with alkyl halides or acid chlorides, in the presence of anhydrous aluminium chloride.



By this method all the hydrogen atoms of benzene may be replaced in turn by alkyl groups, although it is often difficult to stop the action at the desired point and to separate the mixture of isomerides formed. The reaction is still further complicated by the fact that the aluminium chloride tends to detach the alkyl groups already introduced, and in the case of polyalkylated benzenes to promote molecular rearrangement into more stable isomerides.¹

In spite of these drawbacks, however, the Friedel-Crafts reaction has proved of great value in the synthesis of benzene homologues and other aromatic compounds. The Friedel-Crafts reaction is now one of industrial importance and many compounds such as ethylbenzene, benzophenone, acetophenone, phenylethyl alcohol are obtained by this process.

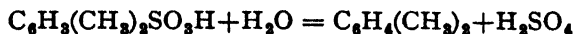
The efficacy of the Friedel-Crafts reaction is dependent on many factors, purity of the aluminium chloride, nature of the solvent, etc., and like most aromatic reactions is subject to the influence of substituents.

¹ See G. Raddley and I. Kanner / 1925. 202

Nitro compounds do not take part in the reaction and for this reason nitrobenzene is often used as a solvent. Groups such as the methoxy, on the other hand, facilitate the process. In general *o-p* directing groups show an activating and *m*-directing a deactivating influence.

Primary amines do not react as they form complex products with aluminium chloride. Phenols form products of the type ROAlCl_2 , which are insoluble in organic solvents and do not readily undergo further reaction. Summarising, it may be said that aromatic hydrocarbons, phenolic ethers, and tertiary amines such as *N*:*N*-dimethylaniline undergo the Friedel-Crafts reaction readily; nuclear substituted halogen compounds with difficulty; and aldehydes or ketones, nitro compounds, carboxylic acids and their derivatives not at all.

5. Benzene and its homologues may also be regenerated from the corresponding sulphonic acids by heating them with superheated steam in the presence of sulphuric acid, concentrated hydrochloric acid or phosphoric acid.



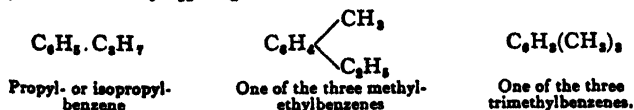
This reaction often provides a convenient method of separating a mixture of hydrocarbons. If, for example, one hydrocarbon can be sulphonated under certain conditions and another not, the latter can easily be extracted from the reaction mixture and the sulphonic derivative of the former then converted back into the hydrocarbon by the above means.

Properties and Reactions of the Alkyl-benzenes

The alkyl-benzenes are generally colourless liquids with a smell like that of benzene. They are insoluble in water but soluble in alcohol and ether. The introduction of a methyl group into the nucleus raises the boiling-points of the methylbenzenes about 24° to 30° ; if introduced into the side chain the rise is about 24° . Towards sulphuric acid and concentrated nitric acid they behave like benzene, the hydrogen of the nucleus undergoing substitution.

A characteristic property of these hydrocarbons which is of great value for their identification is their behaviour on oxidation. Treatment with dilute nitric acid, chromic acid mixture, potassium permanganate, or ferricyanide converts each side chain into a carboxyl group (COOH), by the same intermediate steps as in the case of aliphatic compounds. From the number and relative positions of the resulting carboxyl groups it is possible to deduce the number and position of the alkyl radicals originally present.

Thus a hydrocarbon C_9H_{12} might have either of the constitutions



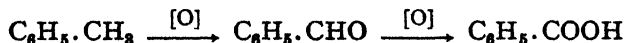
On oxidation, the first compound yields benzoic acid, $\text{C}_6\text{H}_5 \cdot \text{COOH}$; each of the three methyl-ethyl-benzenes gives a different dicarboxylic acid, $\text{C}_6\text{H}_4(\text{COOH})_2$, and each of the three trimethylbenzenes a different tricarboxylic acid, $\text{C}_6\text{H}_3(\text{COOH})_3$.

Toluene, methylbenzene, $C_6H_5.CH_3$, occurs among the products of dry distillation of a number of substances, particularly of Tolu balsam (*Toluifera balsamum*), from which Berzelius first derived its name.

It may be obtained synthetically according to the foregoing methods, (1) by the action of sodium on a mixture of methyl iodide and bromobenzene in dry ethereal solution, (2) by leading methyl chloride into benzene in the presence of aluminium chloride, (3) from phenyl magnesium bromide and dimethyl sulphate in dry ethereal solution, and (4) by the dry distillation of a mixture of sodium benzoate and sodium acetate. Toluene may also be prepared from toluene sulphonic acids and by the distillation of *p*-toluic acid.

On the technical scale coal tar was formerly the only source of toluene, but recently considerable quantities have been obtained from coal gas; by the cyclisation of petroleum hydrocarbons (see p. 116); or by the isolation of toluene from petroleum.

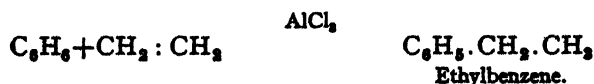
Toluene is a colourless, mobile and strongly refractive liquid, which freezes at -94° and boils at 110° . It is practically insoluble in water but it readily mixes with alcohol, ether and chloroform. Toluene is oxidised by dilute nitric acid to benzoic acid, but with suitable reagents benzaldehyde is obtained (p. 520).



The action of chlorine on toluene varies with the temperature. At higher temperatures substitution occurs in the side chain, and at low temperatures in the nucleus. Chlorine passed into boiling toluene leads first to the formation of benzyl chloride, $C_6H_5.CH_2Cl$, which then yields benzal chloride, $C_6H_5.CHCl_2$, and finally benzo-trichloride, $C_6H_5.CCl_3$. In the cold, on the other hand, *o*- and *p*-chlorotoluenes, $C_6H_4Cl.CH_3$, are formed. On nitration, toluene yields a mixture of the three possible mono-derivatives, chiefly the *o*- and *p*-compounds, with a considerably smaller proportion of *m*-nitrotoluene.

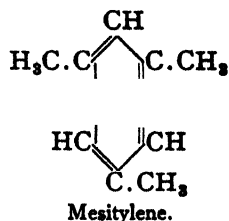
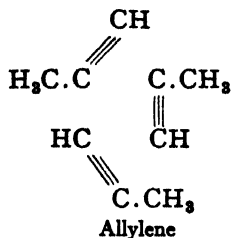
Xylenes, dimethylbenzenes, $C_6H_4(CH_3)_2$, are found in coal tar, *m*-xylene being present in the greatest proportion. *o*-Xylene is obtained from *n*-octane and *p*-xylene from petroleum. *o*-Xylene is used in the manufacture of vitamin B₁₂, and *p*-xylene is in great demand for the preparation of terephthalic acid required for the manufacture of terylene.

Ethylbenzene is prepared industrially in huge quantities, as it is an intermediate in the manufacture of styrene required for synthetic rubber. It is prepared by the interaction of benzene and ethylene in presence of aluminium chloride (*Friedel-Crafts reaction*)



Other catalysts such as phosphoric acid can be used if the reaction is carried out under pressure at $300^\circ C$.

Trimethylbenzenes, $C_6H_3(CH_3)_3$. Of these, hemimellitol (1 : 2 : 3) boils at 175° , pseudocumene (1 : 2 : 4) at 170° , and mesitylene (1 : 3 : 5) at 164° . All three occur in coal tar. Mesitylene is formed by the action of concentrated sulphuric acid on acetone or allylene, $3CH_3.CO.CH_3 = C_6H_3(CH_3)_3 + 3H_2O$.



The proof of its symmetrical structure was of great importance in determining the orientation of benzene substitution products.

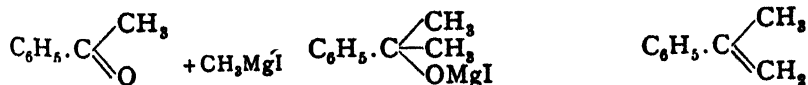
Cymene, *p*-methyl-isopropyl-benzene, $CH_3.C_6H_4.CH(CH_3)_2$ is found in various ethereal oils (oil of thyme and oil of eucalyptus), and may be obtained from camphor, oil of turpentine and certain other terpenes. It is a pleasant-smelling liquid, which boils at 175° . It is manufactured by heating camphor with phosphorus pentoxide.

Cumene, $C_6H_5.CH(CH_3)_2$, *isopropylbenzene*, is usually obtained from coal tar.

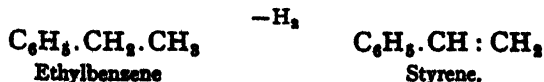
Benzene Hydrocarbons with Unsaturated Side Chains

These show, on the one hand, the properties characteristic of aromatic compounds, and on the other those of the unsaturated hydrocarbons of the aliphatic series (see p. 119). They readily unite with hydrogen and halogens.

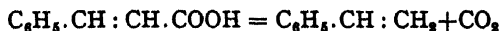
Alkylene benzene derivatives can be prepared by means of the Grignard reaction, either directly or by the elimination of water from the carbinols obtained in such variety by this reaction from aldehydes, ketones, esters and alkyl halides. Their direct formation occurs particularly in those cases where an excess of the Grignard reagent is employed, and the reaction mixture, after evaporation of the ether, is heated for some time, *e.g.*,



Styrene, *vinylbenzene*, $C_6H_5.CH : CH_2$, is the simplest representative of the aromatic olefine derivatives. It is present in storax and is a colourless, strongly refracting liquid, b.p. 146° , with a smell resembling that of benzene. It is manufactured from ethylbenzene (p. 456) by dehydrogenation by means of a catalyst or superheated steam.



It is prepared in the laboratory by the dry distillation of cinnamic acid in the presence of a trace of hydroquinone.



This is an example of the use of decarboxylation in preparative work. Styrene can also be prepared by removal of hydrochloric acid from chloroethylbenzene. At 200° it polymerises to a solid compound called metastyrene. On reduction it yields ethylbenzene, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_3$. Styrene is used in the manufacture of plastics. It is of interest that styrene in 1922 was a laboratory curiosity worth probably about one hundred pounds per 25 grams. Now it is produced by the ton.

The presence in styrene of a double bond conjugated with the benzene nucleus can be detected by the ultra-violet absorption spectrum of the compound. Benzene derivatives with unsaturated groups whose double bonds are not conjugated with the benzene ring have absorption curves similar to that of benzene with the corresponding alkyl side-chain. Thus allyl-benzene, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}:\text{CH}_2$ and ethylbenzene have very similar spectra. On the other hand benzene derivatives with side-chains containing double bonds conjugated with the nucleus show considerable differences. Styrene, for example, has a spectrum quite different from that of ethylbenzene.

V

Halogen Derivatives of the Aromatic Hydrocarbons

Benzene and its derivatives give rise to three types of halogen-compounds: nuclear substituted halogen-compounds, side-chain substituted compounds, and substances such as benzene hexachloride in which halogen adds on to the benzene nucleus. Of these, the first type is the most important and will be described first.

Aryl Halides

Substances such as chlorobenzene, $\text{C}_6\text{H}_5\text{Cl}$, or chlorotoluene, $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{Cl}$, which contain one or more nuclear hydrogen atoms replaced by halogen are known as *aryl halides*. They can be readily prepared by the following methods.

(1) One of the characteristics of the benzene ring is the ease with which it undergoes substitution by chlorine or bromine, particularly in the presence of a catalyst or *halogen carrier* such as iron, iodine, aluminium

chloride, etc. Chlorobenzene, for instance, is prepared commercially by the direct chlorination of benzene in the presence of ferric chloride.

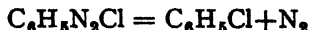


Direct iodination is not so straight forward since the hydriodic acid set free during the reaction must be removed as fast as it is formed. The hydrocarbon is therefore heated with iodine and an oxidising agent such as mercuric oxide or iodic acid. Trifluoroacetyl hypoiodite, generated from silver trifluoroacetate and iodine, is also a useful iodinating agent.¹



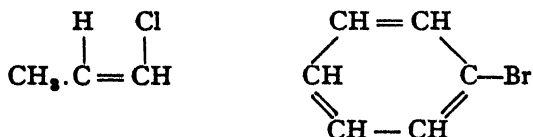
It has already been mentioned in discussing toluene that chlorine and bromine may enter either the side-chain or the nucleus, according to experimental conditions.

(2) Halogeno-compounds are frequently obtained from diazo-compounds (see p. 478) by interaction with cuprous chloride or bromide, or with potassium iodide.



(3) Other methods include bromination by means of hypobromous acid (p. 441).

Properties.—In their chemical behaviour the aryl halides are distinguished above all by the stability of the halogen atom. This halogen cannot be exchanged readily for other groups such as OH and NH₂, as in the saturated aliphatic derivatives, but resembles the relatively non-reactive halogen linked to an unsaturated carbon atom in an ethylene compound (p. 140). This inertness of the halogen atom attached to the nucleus is exemplified by the failure of boiling ethanolic potassium hydroxide to remove bromine from bromobenzene or bromotoluene.

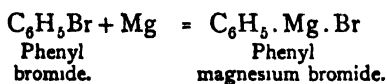


Nuclear halogen, however, can be activated by the influence of other substituents present in the ring. For example, the occurrence of a nitro-group in the ortho- or para-position to the halogen atom increases the reactivity of the latter (p. 466) so that the chlorine reactivity of picryl chloride (1-chloro-2:4:6-trinitrobenzene) resembles that of an acid chloride.² Similarly, bromine in *o*-bromobenzoic acid is very reactive in the presence of copper acetate or copper powder. When an aqueous solution of the acid is boiled for a short time with a mixture of sodium acetate and copper acetate it is converted into salicylic acid. With sodium malonic ester in the presence of copper powder, the acid yields *o*-carboxy-

¹ A. L. Henne and W. F. Zimmer, *J.A.C.S.*, 1951, 73, 1362. ² J. Kenner and collaborators, *J.*, 1914, 105, 2717 and onwards.

phenyl-malonic ester. Under these conditions the chloro-acid is non-reactive. In certain cases halogen attached directly to the nucleus may be brought into reaction by the use of catalysts or ultra-violet radiation.

It is of considerable importance from the practical standpoint that aromatic compounds with halogen in the nucleus readily react with or in presence of certain metals. The *Fittig* synthesis has already been mentioned (p. 454), as well as the *Grignard reaction* in which the aryl halides in dry ethereal solution with metallic magnesium form compounds of the general formula $R.Mg.Hal$ (see p. 142). Like the aliphatic

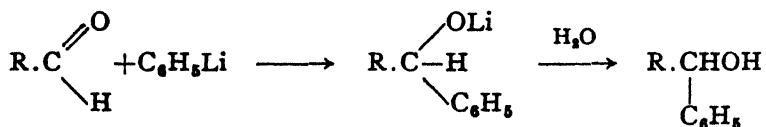


organomagnesium halides, these have been employed with striking success in synthesis, and numerous examples of their use will be found in the following pages.

Aryllithium compounds, soluble in ether, are prepared by treating aromatic chloro- or bromo-compounds in ether solution with two equivalents of lithium.



Like the Grignard reagents, these lithium compounds are very active and are used in synthetic work. For example, with aldehydes they yield secondary alcohols.



Aryl halides can be converted into nitriles by means of cuprous cyanide in quinoline at a temperature above 200° (*Rosenmund reaction*), and the method is frequently used to prepare the less accessible nitriles. 1-Bromonaphthalene in this way yields 1-naphthonitrile.

In general, however, nuclear halogen is inert and this characteristic is used in its detection and differentiation from side-chain halogen which is very reactive (p. 462). Oxidation is also used to determine whether halogen in an aromatic compound is attached to the ring or to the side-chain. For example, *o*-chlorotoluene and its isomer, benzyl chloride, on oxidation yield *o*-chlorobenzoic acid and benzoic acid respectively. Side-chain halogen is thus removed by oxidation while nuclear halogen remains.

Chloro-, bromo-, and iodo-benzene are colourless liquids of characteristic odour, which boil at 132° , 156° , and 189° respectively. Bromobenzene is prepared readily by the bromination of benzene with iron wire as a catalyst. Considerable quantities of *p*-dibromobenzene

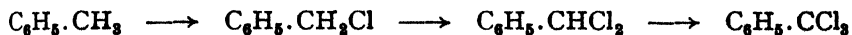
are formed at the same time and are readily separated from the bromobenzene by the making use of the fact that *p*-dibromobenzene in contrast to the mono-compound is less volatile in steam. *o*- and *m*-Dibromobenzene are prepared by diazotising the corresponding bromoaminobenzenes. Iodobenzene is best obtained from aniline by means of the diazo reaction.

Chlorobenzene is used commercially in the preparation of phenol (p. 501), and *p*-dichlorobenzene is sold as a moth killer.

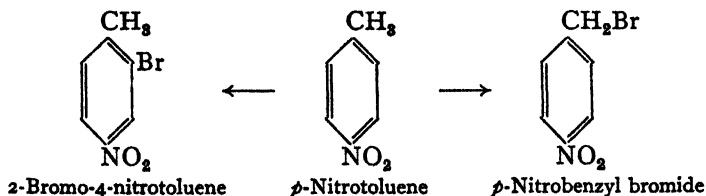
The chlorotoluenes (*o*-, *m*-, and *p*-) are obtained from the corresponding aminotoluenes or toluidines.

Side-Chain Halogenation

It has already been stressed that hydrocarbons such as toluene may undergo halogenation either in the nucleus as described above or in the side-chain. The latter process is exemplified by the side-chain chlorination of toluene which is carried out technically by passing chlorine into boiling toluene.



The path taken by the halogenation of aromatic compounds is greatly influenced by the presence of catalysts and particularly of peroxides. *p*-Nitrotoluene and bromine with antimony tribromide as catalyst give *p*-nitrobenzyl bromide but with ferric bromide as catalyst the product is 2-bromo-4-nitrotoluene.¹



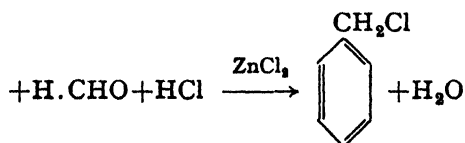
The Peroxide Effect.²—Thanks largely to the researches of Kharasch and his collaborators in the University of Chicago, it has been established that the presence of peroxides such as benzoyl peroxide exerts a remarkable influence on the course of many reactions.³ This is well exemplified by the action of sulphuryl chloride on aromatic compounds. Until recently this reagent was used only for nuclear chlorination, sometimes in the presence of a halogen carrier; toluene, for instance, gives a mixture of *o*- and *p*-chlorotoluene and on further chlorination 2 : 4-dichlorotoluene, tri- and tetrachlorotoluenes, and finally pentachlorotoluene. Peroxide-free toluene does not react to any appreciable extent with sulphuryl chloride in the dark, but a vigorous reaction occurs when a small amount of a

¹ C. W. K. Cavill, *J. Soc. Chem. Ind.*, 1946, 65, 124. ² A review of the subject is given by J. C. Smith, *Ann. Reports*, 1939, 36, 219. ³ Kharasch and Mayo, *J.A.C.S.*, 1933, 55, 2468, and later papers.

peroxide is added. A quantitative yield of benzyl chloride may readily be obtained in this way. Further chlorination gives benzal chloride, but benzotrichloride cannot be prepared by this method.

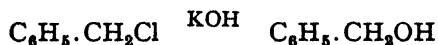
It is thought that the main effect of added peroxides in chlorination by sulphuryl chloride is the formation of chlorine *atoms* which have a greater affinity for aliphatic than for aromatic carbon.

Chloromethylation.¹—A method whereby the chloromethyl group, CH_2Cl , can be introduced into aromatic compounds is by the interaction with formaldehyde and hydrogen chloride. In some cases a catalyst such as zinc chloride is necessary, but in others the mineral acid alone is sufficient. Benzyl chloride may be obtained in 79 per cent. yield by the chloromethylation of benzene.

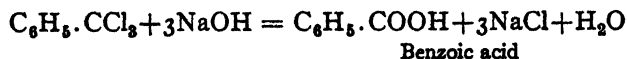
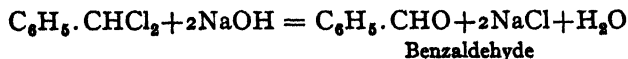


Chloromethylation is much used in synthetic work as the CH_2Cl group can be converted into other groups such as CH_2OH , CH_2CN , and CH_3 .

Halogen in the side-chain is extremely reactive and thus differs strikingly from halogen attached to the nucleus. It is hydrolysed by alkali. Benzyl chloride thus gives benzyl alcohol :



Benzyl chloride is a colourless liquid, b.p. 178° , which has a powerful irritant action on the eyes and nose. It is used in the preparation of benzyl derivatives such as benzyl alcohol and benzylamine. **Benzal chloride** or **benzylidene chloride**, $\text{C}_6\text{H}_5.\text{CHCl}_2$, b.p. 207° , on hydrolysis yields benzaldehyde, and benzotrichloride similarly gives benzoic acid.



Both these processes are used on the industrial scale and are also of value for identification purposes.

As mentioned above the position of halogen atoms in aromatic compounds can be ascertained by oxidation. For example, a substance, $\text{C}_7\text{H}_5\text{Cl}_2$, which on oxidation yields *o*-chlorobenzoic acid must be *o*-chlorobenzyl chloride, $\text{o-Cl.C}_6\text{H}_4.\text{CH}_2\text{Cl}$.

¹ "Chloromethylation of Aromatic Compounds," R. C. Fuson and C. H. McKeever, in *Organic Reactions* (ed. by Roger Adams), 1, 63.

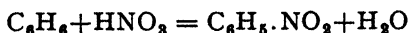
VI

Nitrogen Derivatives of the Aromatic Hydrocarbons

In this section the technically valuable nitro- and amino-compounds are described first, followed by the intermediate products formed during the reduction of nitro- to amino-compounds. Chief among the latter are nitroso- and β -hydroxylamine derivatives and azoxy-, azo- and hydrazo-compounds. After these the diazo-compounds and hydrazines are treated, and finally the azo-dyes, which contain a variety of other groups in addition to nitrogen.

I—NITRO-COMPOUNDS

Preparation.—On account of their practical value the nitro-compounds are of outstanding importance. As has already been stated (p. 453), they are readily formed from aromatic hydrocarbons by the action of concentrated nitric acid.



In a similar manner all kinds of aromatic derivatives, such as phenols, amines, aldehydes and acids, can be nitrated. The elimination of water is usually hastened by the addition of concentrated sulphuric acid to the nitric acid, and the reaction may be carried out either by adding the substance to be nitrated to the mixture of acids, or by allowing nitric acid to run into a solution of the substance in sulphuric acid. The nitro-compounds can be isolated from the reaction mixture by dilution with water, in which they are generally insoluble or sparingly soluble.

Nitration is the most intensively studied of all aromatic reactions and its mechanism is now understood (see p. 440).¹

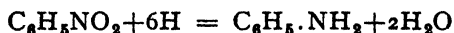
Although there is no difficulty in replacing all the hydrogen atoms in benzene with chlorine or bromine, it has not yet been found possible to effect the direct introduction of more than three nitro groups into benzene or its derivatives. In the alkyl benzenes, the more alkyl groups there are attached to the nucleus the more readily nitration proceeds. Where only one alkyl radical is attached to the ring, the nitro group tends to assume the ortho- or para- but not the meta-position. Thus toluene yields *o*- and *p*-nitrotoluenes, but little *m*-nitrotoluene. The presence of a hydroxyl group in the nucleus also exerts a directive influence towards the *o*- and *p*-positions, *e.g.* phenol gives *o*- and *p*-nitrophenols. On the other hand, in compounds containing the radicals —CHO, —COOH, or —CN, the nitro group tends to assume the meta-position. Similarly, when one nitro group is already present, a second generally enters in the meta-position.

¹ R. J. Gillespie and D. J. Millen. *Quart. Rev.*, 1948, 2, 277.

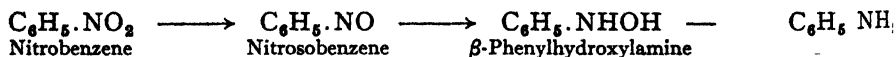
Properties and Reactions.—The nitro-compounds are liquids or crystalline solids, the majority of which are yellow in colour. They are only very slightly soluble in water, but in organic solvents, such as alcohol and ether, they usually dissolve readily. Many of them are volatile in steam. Their boiling-points lie higher than those of the parent hydrocarbons. When treated with sodium or potassium alcoholates the almost colourless trinitrobenzenes form dark red addition compounds, the constitution of which has not yet been determined. In the mono-substituted derivatives the nitro group is firmly united to the nucleus and cannot be directly exchanged for other atoms or groups. In the polynitro-compounds or halogen-substituted nitro-compounds, on the other hand, the nitro groups are more mobile, and one of them can often be replaced by other radicals.

Behaviour of the Nitro-compounds on Reduction

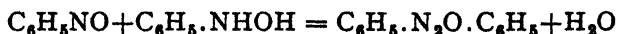
The behaviour of the aromatic nitro-compounds on reduction is of great practical and theoretical interest. When reduced by purely chemical methods the final products, as in the case of the aliphatic derivatives, are amino-compounds.



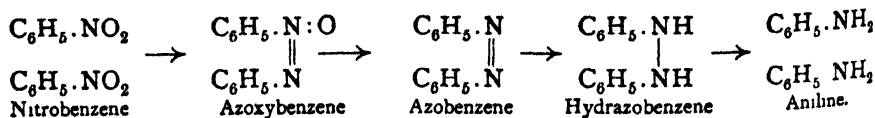
The reaction, however, proceeds in several stages, and intermediate products are formed which may be isolated. One of the factors greatly influencing the course of reduction is the acidity or alkalinity of the solvent during the reaction. By the reduction of nitrobenzene in acid or neutral solution, Bamberger showed that the mono-nuclear intermediate products, *nitrosobenzene* and *phenylhydroxylamine*, are first formed, and that these on further reduction yield aniline.



The reaction, however, may take another path. The nitrosobenzene and phenylhydroxylamine can condense to yield azoxybenzene according to the equation :



The azoxybenzene can undergo further reduction to give *azoxybenzene*, *azobenzene*, *hydrazobenzene*, and finally aniline.

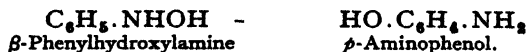


There is evidence that the reduction of nitrobenzene to aniline by titanous chloride proceeds mainly by this route.¹

When the reduction is effected in alkaline solution azoxybenzene, etc., are obtained.

¹ S. A. Newton. Ir.. F. I. Stubbs and C. Hinshelwood. *J.*, 1953, 3384.

The course of the electrolytic reduction of aromatic mononitro-compounds was carefully investigated by Haber. Once again employing nitrobenzene as our example, the main stages of the reduction in both alkaline and acid solution are: nitrobenzene \longrightarrow nitrosobenzene \longrightarrow phenylhydroxylamine \longrightarrow aniline. Secondary reactions, as before, play a considerable part. In weakly acid solution nitrobenzene gives aniline in good yield, but in strongly acid solution *p*-aminophenol is produced, owing to the β -phenylhydroxylamine undergoing intramolecular rearrangement.



In an alkaline medium nitrosobenzene unites with β -phenylhydroxylamine, as described above, to form azoxybenzene, which reduces further to hydrazobenzene. The latter, by atmospheric oxidation, yields a little azobenzene, and on continued reduction is converted into aniline.

Nitration of Benzene and Toluene

It has already been stated that the presence of a meta-directing group in aromatic compounds hinders further substitution. This inhibiting effect is shown by the nitration of benzene, concentrated nitric acid and concentrated sulphuric acid giving nitrobenzene or *m*-dinitrobenzene, according to the concentration of the nitric acid and the temperature used. Further nitration to 1 : 3 : 5-trinitrobenzene, however, occurs only with difficulty and the yields are poor.

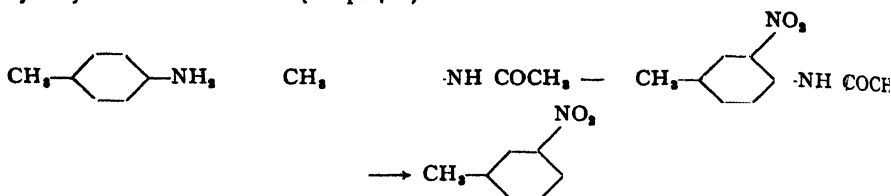
Nitrobenzene, $\text{C}_6\text{H}_5\cdot\text{NO}_2$, *oil of mirbane*, is prepared technically by running a nitrating mixture, composed of 105 parts of nitric acid and 160 parts sulphuric acid with continuous stirring into benzene. Nitrobenzene separates as an upper layer above the denser acid, and is removed, washed with water, and distilled in steam. It is a yellow, strongly refractive liquid (b.p. 208° , m.p. 5°), which like benzaldehyde has a smell resembling that of bitter almonds, and is used chiefly in industry for the preparation of aniline, and in the manufacture of perfumes and perfumed soaps.

***m*-Dinitrobenzene** is obtained as described above and is used for the production of *m*-nitraniline and *m*-phenylenediamine. ***o*-Dinitrobenzene** is obtained from *o*-nitraniline by forming the diazonium cobaltinitrite and decomposing it with a solution of sodium nitrite in presence of cuprous oxide and cupric sulphate. ***p*-Dinitrobenzene** is prepared in excellent yield by the oxidation of *p*-nitraniline by perfluoroacetic acid, $\text{CF}_3\cdot\text{CO}_2\text{H}$.¹

1 : 3 : 5-Trinitrobenzene is best prepared by the oxidation of 1 : 3 : 5-trinitrotoluene to 1 : 3 : 5-trinitrobenzoic acid which is very easily decarboxylated to trinitrobenzene by heating its sodium salt in aqueous solution.

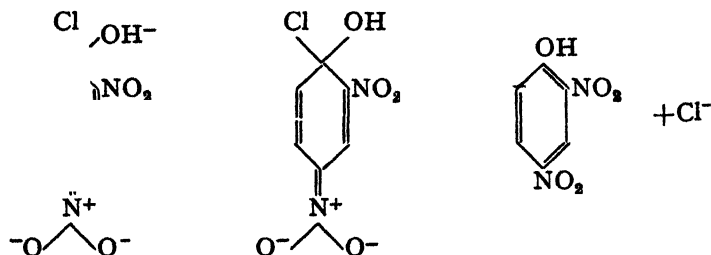
¹ W. D. Emmons and A. F. Ferris, *J.A.C.S.*, 1953, 75, 4623.

Nitrotoluene, $\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{NO}_2$. Toluene on nitration yields a mixture of *o*- and *p*-nitrotoluenes containing a little of the *m*-compound. These can be separated by fractional distillation. *o*-Nitrotoluene, b.p. 218° , gives *o*-nitrobenzaldehyde on oxidation and is also used in the preparation of *o*-nitrobenzyl chloride and *o*-toluidine. *p*-Nitrotoluene, b.p. 230° and m.p. 54° , is converted by the action of fuming sulphuric acid into *p*-nitrotoluene-*o*-sulphonic acid, which is used in the preparation of the dyestuff Direct Yellow. Pure *m*-nitrotoluene, m.p. 16° , b.p. 230° , is best prepared indirectly by nitration of *p*-acetotoluidide and subsequently removing the acetyl amino group by hydrolysis and diazotisation (see p. 480).



On further nitration the *o*- and *p*-nitrotoluenes first yield a mixture of 2 : 4- and 2 : 6-dinitrotoluenes and finally T.N.T. or *s*-trinitrotoluene. The last is a valuable explosive. *Amatol* is an explosive containing a mixture of T.N.T. with ammonium nitrate.

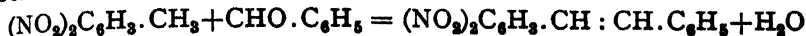
Halogeno-nitrobenzenes.—The inertness of the nuclear halogen in substances such as chlorobenzene and bromobenzene has already been mentioned. When, however, a nitro group is introduced into halogenated benzenes so that it is situated *ortho* or *para* to the halogen, the latter becomes mobile and reactive. The chlorine in *o*- or *p*-chloronitrobenzene and particularly in polynitro compounds such as 1-chloro-2 : 4-dinitrobenzene or picryl chloride is reactive towards alkali, ammonia, amines etc. Heating 1-chloro-2 : 4-dinitrobenzene with alkali, for instance, yields 2 : 4-dinitrophenol. This effect can be traced to the nitro-group which as we have seen (p. 445) causes a marked electron deficiency in the *o*- and *p*-positions. These positions are in consequence open to nucleophilic attack. The formation of the dinitrophenol in the example just given is therefore due to nucleophilic attack by the hydroxyl anion at the positive chlorine-bearing carbon atom to give an intermediate quinonoid derivative, which by loss of a chloride ion yields the dinitrophenol.



Other examples of the reactivity of aromatic halogeno-nitro compounds are given in the formation of picramide (p. 507), and 2 : 4-dinitrophenyl hydrazine (p. 487).

The activation of nuclear halogen atoms by nitro groups in the *ortho* and *para* positions noted above is paralleled by the activation of

methyl groups is observed in *o*-nitro-, *p*-nitro- and especially 2 : 4-dinitro-toluene. While the methyl groups in toluene and *m*-nitrotoluene are quite inert towards reagents such as benzaldehyde, 2 : 4-dinitrotoluene condenses with benzaldehyde in the presence of alkali to give 2 : 4-dinitrostilbene.



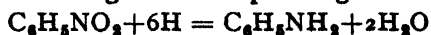
Such reactivity is to be expected from the theory of vinylogy (p. 572), since *o*- and *p*-nitrotoluene are vinylogues of nitromethane in which the methyl group is very reactive.

II.—AMINO DERIVATIVES OF BENZENE

The aromatic amines may be derived theoretically from ammonia in the same manner as the aliphatic amines. In the true aromatic derivatives the nitrogen is attached directly to the benzene nucleus, as in $\text{C}_6\text{H}_5\cdot\text{NH}_2$ and $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_3$. When, however, the amino group is linked to a carbon atom of the side chain in an alkylbenzene, as in the case of $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{NH}_2$, we are dealing with a substituted aliphatic amine, with properties like those of the alkyl amines. The true aromatic amines undergo many of the reactions given by the fatty amines (p. 177, *et seq.*), but differ from the latter in a number of points. For example, the aromatic derivatives are weaker bases than those of the aliphatic series, owing to the acidic character of the phenyl group. In addition, primary and tertiary aromatic amines differ from the corresponding aliphatic compounds in their behaviour towards nitrous acid.

1. Primary Monamines

Methods of Formation.—(1) The primary aromatic amines are almost always prepared by reducing the corresponding nitro-compounds.



This can be effected in various ways, such as by the use of zinc and hydrochloric acid, tin or stannous chloride and hydrochloric acid, iron and hydrochloric acid, alcoholic ammonium sulphide, or by electrochemical methods. In many cases reduction may be carried out very conveniently at ordinary temperatures by use of hydrogen and *Raney nickel catalyst*,¹ which is prepared by boiling nickel-aluminium alloy with alkali, when the aluminium dissolves, leaving nickel in a finely divided and highly active state. The intermediate products which are formed under different conditions have already been described in detail in the foregoing pages.

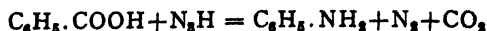
(2) Amines may be obtained from phenols by heating them to 150° with the double compound of zinc chloride and ammonia, ($\text{ZnCl}_2, \text{NH}_3$), *e.g.* $\text{C}_6\text{H}_5\text{OH} + \text{NH}_3 = \text{C}_6\text{H}_5\text{NH}_2 + \text{H}_2\text{O}$. The substitution of an amino-group for a phenolic hydroxyl group or a halogen atom attached to a benzene nucleus takes place more readily when nitro-groups are also present in the compounds.

(3) A rapid and efficient method² of converting an aromatic carboxylic acid into

¹ See, for example, A. Albert and B. Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1940, 74, 74.

² K. F. Schmidt, *Ber.*, 1924, 57, 704. The reaction should be carried out under the draught, as breathing the vapour of hydrazoic acid, even in traces, leads to severe headache.

a primary amine is to treat the acid, dissolved in concentrated sulphuric acid at 45-50° with a solution of hydrazoic acid in chloroform, the addition being made drop by drop over a period of two hours with stirring (*Schmidt Reaction*). Alternatively, the sulphuric acid solution may be covered with a layer of chloroform and concentrated aqueous sodium azide (about 20 per cent. excess) added slowly under the same conditions. The mixture is finally run on to ice. Yields by this method are usually very high.



(4) Among other methods of preparing higher homologues of aromatic amines may be mentioned one discovered by A. W. Hofmann. When the salts of *N*-alkylanilines are heated in closed vessels at 250-300° they undergo the *Hofmann-Martius rearrangement*, whereby the alkyl groups migrate to the *o*- and *p*-positions. Ethylaniline hydrochloride, for example, undergoes the following change :



It should be noted that this reaction is not only of scientific interest, but is also of great practical value. It is employed on the technical scale for the production of the aniline homologues required in the dyestuff industry.

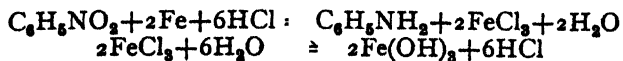
Properties and Reactions.—The primary monamino-compounds are colourless liquids or solids, which are volatile with steam and can be distilled without decomposition. As already mentioned, they are weak bases (pK_a 4.6) which do not give an alkaline reaction. With the entrance of electro-negative groups such as Cl and NO_2 into the nucleus, the basic character becomes still weaker, and the salts of these substituted anilines are either dissociated with water or incapable of existence. From the chemical point of view the primary aromatic amines resemble the fatty compounds in their behaviour towards alkylating agents, acid chlorides, aldehydes and chloroform (see p. 137). They differ mainly in their reaction with nitrous acid, which in acid solution converts them into diazo-compounds. In the amino-benzenes the nuclear hydrogen is far more readily substituted than in benzene itself, and in the same way the amines are much more susceptible to oxidation than the hydrocarbons. The various products obtained by the above reactions are described in detail under aniline.

Aniline and its Derivatives

Aniline, $\text{C}_6\text{H}_5\cdot\text{NH}_2$, is prepared technically from nitrobenzene. The latter is mixed with a little water in a cast-iron vessel provided with stirring apparatus and a reflux condenser. Steam is led in to

¹ A similar migration of alkyl groups has been observed with derivatives of other cyclic bases, such as pyridine, pyrazine, pyrrole and pyrazole. For the mechanism of this change, which is assumed to involve the separation of the alkyl group as a positive ion, see H. B. Watson, *Ann. Reports*. 1930. 204.

warm the mixture, to which iron filings and hydrochloric acid are then added. Only a small proportion (about $\frac{1}{10}$) of the amount of acid required by the first equation is needed in actual practice, because the ferric chloride formed undergoes hydrolysis to ferric hydroxide and hydrochloric acid. The latter again reacts with iron with the result that



a small amount of acid acts as a carrier in the reduction by iron and water. At the end of the reaction milk of lime is added, in order to decompose the aniline hydrochloride formed, and the free aniline is distilled over in steam and fractionated *in vacuo*. For the intermediate stages in this reduction see p. 464.

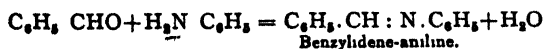
When reduced with concentrated hydrochloric acid and other metals, nitrobenzene yields aniline containing chloraniline. The proportion of the latter has been found to vary from 3 per cent. with tin to 26 per cent. with zinc.¹

In the pure state aniline is a colourless, strongly refractive liquid which boils at 189° . It is only sparingly soluble in water and is poisonous. Aniline is detected by the deep violet colour it gives in aqueous solution with bleaching powder (*Runge* test).

It will be anticipated that aniline will be a very reactive substance which readily undergoes substitution in the *o*- and *p*-positions (p. 444). This is borne out in practice, aniline with bromine water, for example, yielding 2 : 4 : 6-tribromaniline. Mono- and di-substitution products can be obtained by acetylating or benzoylating the amino-group before bromination. Acetanilide with bromine in acetic acid gives *p*-brom-acetanilide, from which *p*-bromaniline can be obtained by hydrolysis.

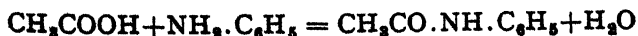
The most important salt of aniline is the readily soluble hydrochloride, $\text{C}_6\text{H}_5\cdot\text{NH}_2\cdot\text{HCl}$, known technically as *aniline salt*. The sulphate $(\text{C}_6\text{H}_5\cdot\text{NH}_2)_2\text{H}_2\text{SO}_4$ is only sparingly soluble in water.

Aniline reacts with aromatic aldehydes with elimination of water to form *Schiff's* bases or *anils*.



If the hydrogen atoms of the amino-group in aniline are replaced by organic acid radicals, compounds termed **anilides** are produced. These can be prepared by heating aniline salts with the required organic acids, or by the interaction of aniline and an acid chloride or ester. The best known example of this class is acetanilide.

Acetanilide, $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_3$, may be prepared both in the laboratory and on the technical scale by heating acetic acid or acetic anhydride with aniline or aniline acetate.



¹ G. R. Robertson and R. A. Evans, *J. Org. Chem.*, 1940, 5, 142.

It melts at 112° , boils at 304° , and is only very sparingly soluble in cold water, from which it crystallises in small white plates. Acetanilide is employed in medicine as a febrifuge under the name of *antifebrin*.

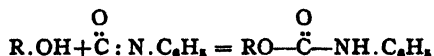
Nitration of Aniline

Nitric acid reacts vigorously with aniline, converting it into resinous products. Hence, in order to obtain mono- and dinitro-derivatives, the amino-group must first be protected. This can be done either by acetylating the aniline before nitration, or by nitrating it with a mixture of nitric acid and much sulphuric acid. In the latter case all three isomeric mono-nitro-compounds are formed together, viz., *o*-nitraniline, m.p. 71° , *m*-nitraniline, m.p. 114° , and *p*-nitraniline, m.p. 147° ; whereas when the aniline is first acetylated the *p*-nitro-compound is the chief product. These nitranilines can also be prepared by the partial reduction of the corresponding dinitrobenzenes by means of ammonium sulphide.

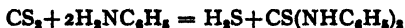
Carbonic Acid Derivatives of Aniline

The anilides of carbonic acid correspond to the urethanes and may be obtained in a similar manner to these (see p. 353).

Phenyl-urethane, $C_6H_5.NH.CO.OC_2H_5$, can be prepared by the action of aniline on chlorocarbonic ester. **Carbanilide** or *sym. diphenyl-urea*, $(C_6H_5.NH)_2CO$, m.p. 235° , and *phenyl-urea*, $C_6H_5.NH.CO.NH_2$, m.p. 144° , are obtained by special methods, e.g. from aniline sulphate and potassium cyanate, or by heating aniline with urea. **Phenyl isocyanate**, $C_6H_5.N:C:O$, b.p. 166° , can be prepared by treating aniline or its hydrochloride with phosgene, or by distilling phenyl-urethane with phosphorus pentoxide. It is a colourless liquid, the vapour of which has a lachrymatory action. Phenyl isocyanate has often been employed in the examination of tautomeric compounds, particularly for showing the presence of a hydroxyl group. The interaction of equimolecular quantities of phenyl isocyanate and a hydroxy derivative leads to the formation of a *phenyl-carbamic ester*, according to the equation :



Thiocarbanilide, diphenyl-thiourea, $(C_6H_5NH)_2CS$, is prepared by boiling aniline with carbon disulphide.



It is obtained in the form of colourless plates, m.p. 154° . When heated with concentrated hydrochloric acid it decomposes into aniline and phenyl isothiocyante (phenyl mustard oil), $C_6H_5.N:C:S$, a colourless liquid of pungent smell.

Monamino Derivatives of Toluene

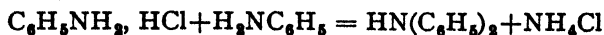
Toluidines, $CH_3.C_6H_4.NH_2$.—The ortho and para derivatives are obtained by reducing the corresponding nitrotoluenes with iron and hydrochloric acid, and are employed in the manufacture of azo- and triphenylmethane dyestuffs. *o*-Toluidine is a liquid, b.p. 197° , and *p*-Toluidine a solid which melts at 45° and boils at 198° . *m*-Toluidine can be prepared from *m*-nitrotoluene (obtained by indirect methods, see p. 446) and is a liquid, b.p. 199° .

Benzylamine, $C_6H_5.CH_2.NH_2$, b.p. 183° , which may be regarded as a phenyl-substituted methylamine, is formed by the methods described under aliphatic amines, e.g. by heating benzyl chloride, $C_6H_5.CH_2Cl$,

with ammonia, or by the reduction of phenyl nitro-methane, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{NO}_2$. It is a colourless liquid, and in its chemical properties resembles methylamine. It dissolves in water to give a strongly alkaline solution (pK_a 9.4) and yields no diazo-compound with nitrous acid.

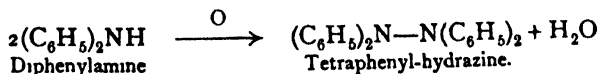
2. Secondary Monamines

Purely aromatic secondary amines may be prepared by heating the primary bases with their hydrochloric acid salts. For example, by heating aniline with aniline hydrochloride at 220° to 230° in an autoclave, **diphenylamine**, $(\text{C}_6\text{H}_5)_2\text{NH}$, is formed.

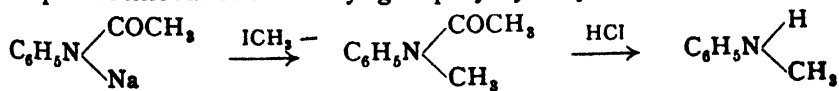


Another method of preparing compounds of this type is by the action of bromobenzene on primary aromatic amines, in the presence of a trace of cuprous iodide as catalyst.¹ Diphenylamine is a colourless crystalline substance, m.p. 54° and b.p. 310° , which is used in the preparation of diamino-diphenylamine and azo-dyes. Its basic properties are so weak that its salts are decomposed with water. On the other hand, the hydrogen of the imino-group is replaceable by metals. With nitrous acid it yields diphenylnitrosamine, $(\text{C}_6\text{H}_5)_2\text{N}\cdot\text{NO}$.

Diphenylamine is rapidly attacked by oxidising agents, yielding a product which gives an intense blue coloration with concentrated sulphuric acid. Hence it is employed for the qualitative detection of nitric and nitrous acids. This behaviour is due to the formation of tetraphenylhydrazine, which gives the above striking colour reaction with concentrated sulphuric acid.²



Secondary *mixed aromatic amines* or phenyl-alkylamines may be prepared from the alkyl iodides and the acetyl derivatives of primary aromatic bases. **Methylaniline**, for example, is formed in this manner by the action of methyl iodide on the sodium salt of acetanilide, and subsequent removal of the acetyl group by hydrolysis :

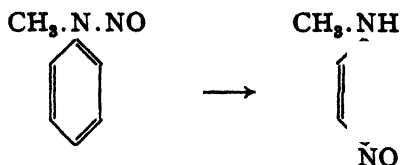


The secondary mixed aromatic amines are stronger bases than the purely aromatic compounds. When treated with nitrous acid they yield nitroso derivatives, $\text{C}_6\text{H}_5\text{N}(\text{R})\cdot\text{NO}$, which with weak reducing agents are converted into hydrazines, $\text{C}_6\text{H}_5\text{N}(\text{R})\cdot\text{NH}_2$, and on energetic reduction regenerate the original secondary amine. The N-nitroso-N-alkyl-anilines when heated with aqueous or ethanolic hydrochloric acid undergo what is termed the *Fischer-Hepp* rearrangement. N-Nitroso-N-methyl-aniline, for example, yields *p*-nitroso-N-methylaniline. There is evidence that

¹ I. Goldberg, *Ber.*, 1907, 40, 4541.
H. W. Schwechten, *Ber.*, 1927, 60, 1203.

² Wieland, *Ber.*, 1906, 39, 1499. E. Weitz and

the reaction proceeds by the formation of *N*-methylaniline and nitrosyl chloride which then recombine to give the *p*-nitroso-compound.¹



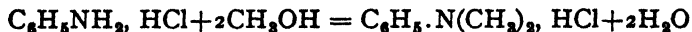
3. Tertiary Monamines

In this case also a distinction must be drawn between compounds of purely aromatic and those of mixed aliphatic-aromatic nature. A point of outstanding interest is the behaviour of phenyl-dialkylamines towards nitrous acid. Whereas tertiary aliphatic amines do not react with nitrous acid at all, mixed amines of the above type are transformed by this reagent into *p*-nitroso-compounds (see below). A small proportion of a nitro derivative is also formed as a by-product.

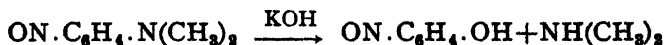
Tertiary phenylamines either fail to react with nitrous acid or undergo nitration in the nucleus.

Triphenylamine, $(\text{C}_6\text{H}_5)_3\text{N}$, can be obtained by the action of bromobenzene on dipotassium aniline, $\text{C}_6\text{H}_5\text{NK}_2 + 2\text{C}_6\text{H}_5\text{Br} = (\text{C}_6\text{H}_5)_3\text{N} + 2\text{KBr}$. It melts at 127° and forms no salts with acids.

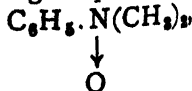
Dimethylaniline, $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$, b.p. 192° , is formed by the methylation of aniline, and is prepared industrially by heating aniline hydrochloride with methyl alcohol in an autoclave.



The resulting hydrochloride of dimethylaniline is treated with milk of lime, and the free base removed by distillation in steam. A number of the characteristic reactions of dimethylaniline depend on the extraordinary mobility of the hydrogen atom in the *para*-position. Thus with nitrous acid it gives *p*-nitrosodimethylaniline, $(\text{NO})\text{C}_6\text{H}_4\cdot\text{N}(\text{CH}_3)_2$, crystallising in green leaves or plates, m.p. 85° . When *p*-nitroso-dimethylaniline is reduced with zinc dust it yields *p*-amino-dimethylaniline, $\text{NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}(\text{CH}_3)_2$, which, like the nitroso-compound, is used in the manufacture of numerous dyes. Another interesting property is the breakdown by alkali to *p*-nitrosophenol and dimethylamine (p. 179).



When treated with an aqueous solution of hydrogen peroxide, dimethylaniline takes up an atom of oxygen to form



dimethylaniline oxide, from which oxygen can readily be removed to give the original base.

¹ P. W. Neber and H. Rauscher, *Ann.*, 1942, 559, 182.

4. Diamines and Polyamines

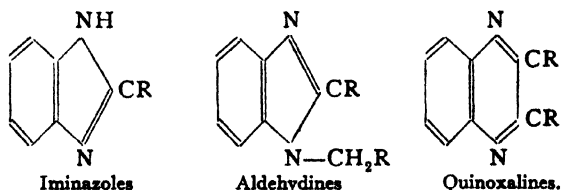
Aromatic diamines may be prepared by the reduction of the corresponding dinitro-, nitroamino-, or aminoazo-compounds.

For example, *m*-phenylene diamine, $C_6H_4(NH_2)_2$, m.p. 63° and b.p. 287° , is obtained by the reduction of *m*-dinitrobenzene with zinc dust and caustic soda, and *o*-phenylene diamine, m.p. 102° and b.p. 252° , in a similar manner from *o*-nitraniline. *p*-Phenylene diamine, m.p. 147° and b.p. 267° , is prepared by reducing aminoazobenzene with tin and hydrochloric acid.



The diamines are solid compounds of strong basic properties. Their reactions differ according to the positions of the amino groups.

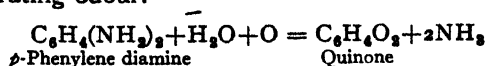
o-Diamines are distinguished by the ease with which they condense with a variety of other compounds to form cyclic derivatives. Thus when heated with organic acids they yield iminazoles, with aldehydes they yield aldehydines, and with 1:2-diketones such as phenanthraquinones they yield quinoxalines.



The quinoxaline reaction is useful as a qualitative test for *o*-diamines as well as for 1:2-diketones.

m-Diamines when treated with nitrous acid give brown dyes—aminoazo-compounds—produced by the condensation of several molecules of the diamine (*Bismarck brown* reaction). The *p*-substituted *m*-diamines do not give this colour test.

The most important reaction of the *p*-diamines is the following. With oxidising agents, *e.g.* when boiled with manganese dioxide and sulphuric acid, they readily pass into quinones, which may be recognised by their penetrating odour.



III.—NITROSO- AND β -HYDROXYLAMINE DERIVATIVES

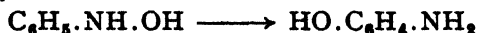
Mononitroso derivatives of the aromatic hydrocarbons are obtained, in general, by the action of certain oxidising agents (cold monopersulphuric acid, or potassium bichromate and sulphuric acid) on the corresponding amino-compounds: $Ar.NH_2 \rightarrow Ar.NH.OH \rightarrow Ar.NO$. Like the aliphatic nitroso derivatives (see p. 169), they are very volatile and exist in different molecular states. The solid aromatic nitroso-compounds are colourless and bimolecular, but in solution, or when fused, the great

majority of them assume a blue or green colour and give molecular weights corresponding to the monomolecular formula Ar.NO . On further oxidation the nitroso-compounds readily pass into nitro-compounds, and on reduction they yield amino-compounds.

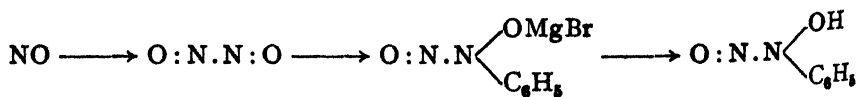
The typical aromatic representative of this class, **nitrosobenzene**, $\text{C}_6\text{H}_5.\text{NO}$, is obtained by oxidising β -phenylhydroxylamine with potassium bichromate and sulphuric acid. It is also formed when aniline is oxidised (*a*) in sulphuric acid solution with potassium permanganate, in the presence of a little formaldehyde, (*b*) with monopersulphuric acid (*Caro*). It crystallises in colourless volatile needles, m.p. 68° , and possesses a powerful characteristic smell. In the molten state or in solution it is emerald green in colour. It is readily oxidised to nitrobenzene or reduced to aniline. Nitrosobenzene condenses with aniline to form azobenzene, and with β -phenylhydroxylamine to form azoxybenzene (see p. 475).

β -Arylhydroxylamines are prepared by reducing aromatic nitro-compounds with neutral reagents such as zinc dust and ammonium chloride solution, or ammonium sulphide. They are also obtained by electrochemical reduction, in which case a cathode solution of acetic acid and sodium acetate dissolved in water or other solvent is best employed. They readily reduce ammoniacal silver solutions and Fehling's solution, and when dissolved in water rapidly take up oxygen from the air, particularly in the presence of alkali. Those β -arylhydroxylamines in which the *p*-hydrogen atom is not substituted are transformed by sulphuric acid into the isomeric *p*-amino-phenols (see below).

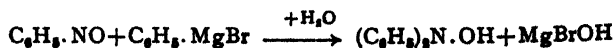
β -Phenylhydroxylamine, $\text{C}_6\text{H}_5.\text{NHOH}$, is obtained by reducing nitrobenzene by the above methods. It is a white crystalline compound, m.p. 81° . The powdered substance induces violent sneezing. Atmospheric oxygen converts it into azoxybenzene, and with more energetic oxidising agents it yields nitrosobenzene. It reduces Fehling's solution and ammoniacal silver nitrate, even in the cold. With acids it combines to form salts, and when warmed with mineral acids is readily isomerised to *p*-aminophenol.



Nitrous acid converts it into a nitroso derivative, $\text{C}_6\text{H}_5.\text{N(NO).OH}$. This *nitrosophenyl-hydroxylamine* is more conveniently obtained by the action of nitric oxide on an ethereal solution of phenyl magnesium bromide:

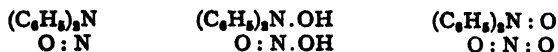


Diphenyl-hydroxylamine, $(\text{C}_6\text{H}_5)_2\text{N.OH}$, is prepared by treating nitrosobenzene with phenyl magnesium bromide:



It is a beautifully crystalline compound which melts with decomposition at 60° , and is of interest in connection with the discovery of divalent nitrogen derivatives.

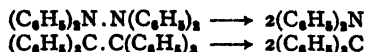
Nitrogen diphenyl, $(C_6H_5)_2N$, and other diaryl derivatives of divalent nitrogen, are formed as a result of the dissociation of tetra-aryl hydrazines. Nitrogen diphenyl bears the same relationship to diphenyl-hydroxylamine as nitric oxide to nitrous acid.



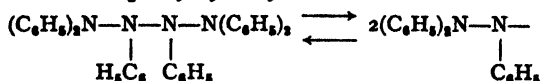
The presence of nitrogen diphenyl in a solution of tetraphenyl-hydrazine can be detected by its unsaturated properties. When, for example, nitric oxide is passed into a solution of the hydrazine in toluene at 90° diphenyl nitrosamine is formed, produced by union of the two divalent nitrogen groups.



The dissociation of tetraphenyl-hydrazine into the free radical $(C_6H_5)_2\dot{N}$ is exactly analogous to the formation of triphenyl-methyl from hexaphenyl-ethane, which will be discussed later.



Another compound which tends to dissociate in solution into a derivative of divalent nitrogen is *hexaphenyl-tetrazane*. In the solid state this is monomolecular, but in solution it largely exists as *triphenylhydrazyl*.

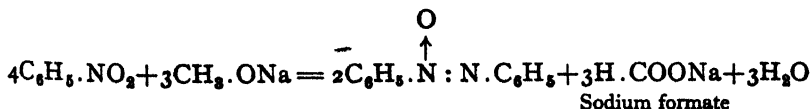


IV.—AZOXY-, AZO- AND HYDRAZO-COMPOUNDS

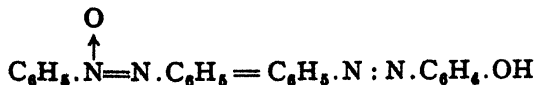
The azoxy-compounds are generally prepared by heating nitro derivatives with an alcoholic solution of sodium methoxide; sodium amalgam, or magnesium and ammonium chloride solution, can also be employed as the reducing agent. They are yellow or red in colour, crystallise well, and on further reduction yield azo-, hydrazo- and amino-compounds. With moderately warm concentrated sulphuric acid they isomerise to *hydroxy-azo-compounds*.

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Azoxybenzene, $C_6H_5.N=N.C_6H_5$, is best prepared by boiling nitrobenzene with a methyl alcoholic solution of sodium methoxide.



It forms pale yellow crystals, m.p. 36° . When warmed with concentrated sulphuric acid it isomerises into *p*-hydroxy-azobenzene.

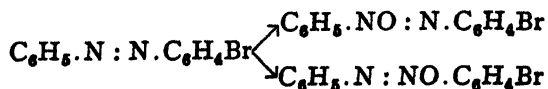


Azoxy-compounds were formerly believed to possess the symmetrical

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structure, e.g. $C_6H_5.N-N.C_6H_5$. An unsymmetrical azo-compound, however, was shown by Angeli to give rise in some instances to two

isomeric azoxy-compounds. The symmetrical formula has therefore been abandoned.

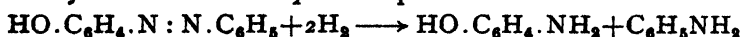


The unsymmetrical structure has also been conclusively proved by polarimetric methods.¹

Azo-compounds may be obtained from nitro-compounds by reduction with sodium amalgam or an alkaline solution of stannous chloride, from azoxy-compounds by reduction, and from hydrazo-compounds by oxidation. As will be seen later, aminoazo-compounds, the amino derivatives of azo-compounds, are formed when hydrochlorides of aromatic amines are warmed with diazoamino-compounds.

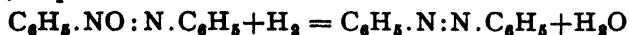
The azo-compounds are red to yellowish-red crystalline substances, which on further reduction yield first hydrazo-compounds and finally amines. They are very stable and may be distilled without decomposition, differing in this respect from the unstable diazo-compounds to be described later, which contain two nitrogen atoms united with one hydrocarbon radical and an acidic atom or group (e.g. $\text{C}_6\text{H}_5\cdot\text{N}_2\cdot\text{Cl}$).

The constitution of azo-compounds and especially of the more complex azo-dyes is readily determined by disruption with reducing agents such as tin and hydrochloric acid or sodium hydrosulphite. Fission occurs at the double bond and two amine fragments result. For example, hydroxy-azobenzene yields aniline and *p*-aminophenol on reduction :

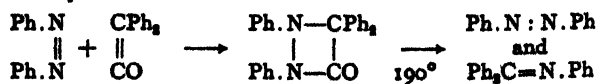


Hence it may be deduced that in the formation of the azo-dye the coupling occurred in the *p*-position to the phenolic —OH group.

Azobenzene, $\text{C}_6\text{H}_5\cdot\text{H} : \text{N}\cdot\text{C}_6\text{H}_5$, is prepared either by the reduction of nitro- or azoxy-benzene with lithium aluminium hydride or by the oxidation of hydrazobenzene with sodium hypobromite. It forms orange-red crystals, m.p. 68°.



In ordinary azobenzene the phenyl groups are arranged in the *trans* positions with respect to the two nitrogen atoms, as is proved by the zero value of the dipole moment. Under the influence of light, especially in the ultra-violet region, the *trans* form in solution is partly converted into the *cis* isomeride (15-40 per cent.), which has a dipole moment of 3.0. *Cis*-azobenzene forms bright red crystals, which melt at 71.4° and at this temperature change comparatively rapidly into *trans* azobenzene.² The two isomerides are conveniently separated by chromatographic adsorption on alumina.³ An interesting chemical difference is that whereas the *trans* compound does not react as such with diphenylketene, the latter combines vigorously with *cis*-azobenzene at ordinary temperatures. The structure of the adduct is shown by its decomposition at 190° to yield both azobenzene and benzophenone-anil.⁴



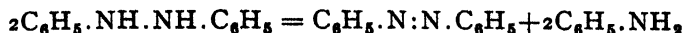
¹ T. T. Chu and C. S. Marvel, *J.A.C.S.*, 1933, 55, 2841. ² G. S. Hartley, *J.*, 1938, 633.

³ A. H. Cook and D. G. Jones, *J.*, 1939, 1309.

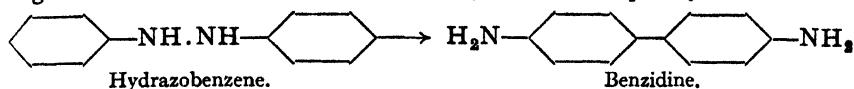
⁴ Cook and Jones, *ibid.*, 1941, 184.

Hydrazo-compounds, $R.NH.NH.R$, are produced by the reduction of azo-compounds with ammonium sulphide, zinc dust and alcoholic potash, sodium amalgam, or sodium amylate. They may also be prepared directly from nitro-compounds by reduction with zinc dust and alkali, or by electrochemical means.

Hydrazobenzene, $C_6H_5.NH.NH.C_6H_5$, forms colourless leaves or plates, m.p. 131° , is very easily oxidised to azobenzene, and with energetic reducing agents yields aniline. When heated, it decomposes into azobenzene and aniline.



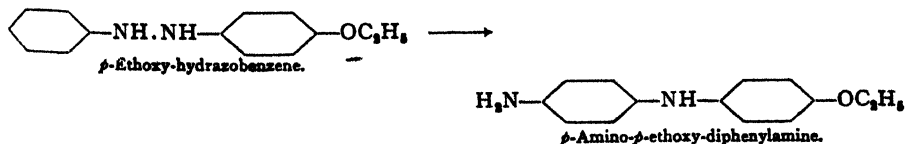
Under the influence of mineral acids hydrazobenzene undergoes a remarkable intramolecular change, the chief product of the reaction being a base known as *benzidine* or 4 : 4'-diamino-diphenyl.



Consequently, when hydrazobenzene is formed by the reduction of azobenzene in acid solution, it is immediately transformed into benzidine. The latter is prepared technically by reducing nitro-benzene to hydrazobenzene by means of zinc dust and sodium hydroxide, and treating the product with acid. Benzidine and its homologue tolidine are of value in the preparation of substantive dyes.

The intramolecular change described above is also undergone by other hydrazo-compounds in which the two para-positions are not substituted, and is known generally as the *benzidine transformation*. A small amount of 4 : 2'-diaminodiphenyl is also formed (*diphenylene transformation*).

It is obvious that this change cannot take place in the same manner if one of the two para-hydrogen atoms of the hydrazo-compound is already replaced by a substituent. The course of the reaction in this case was carefully examined by Jacobson and his co-workers. It results in a semi-benzidine or *semidine transformation*, the products being called semidines, e.g.,



The benzidine transformation is an *intramolecular* change. Support for this was adduced by Ingold and Kidd¹ who found that 2 : 2'-dimethoxy- and 2 : 2'-diethoxy-hydrazobenzene undergo rearrangement of the benzidine type at comparable rates, and *in the same solution* undergo the change independently. Had the change been *intermolecular* some at least of the dissociated fragments would have united to give the mixed benzidine, 2-methoxy-2'-ethoxybenzidine, but no trace of this product could be detected.

¹ C. K Ingold and H. V. Kidd, *J.*, 1933, 984.

V.—DIAZO-COMPOUNDS¹ AND HYDRAZIN

The aromatic diazo-compounds containing the group $\text{—N}_2\text{—}$ are of great importance theoretically as well as practically. They were discovered in 1860 by Griess, as a result of the action of nitrous acid on primary amines of the benzene series. Not only do they afford interesting examples of isomerism, but they are highly reactive and form the starting-point in the preparation of a large number of dye-stuffs.

According to Hantzsch, the diazo-compounds ArN_2X (where Ar is C_6H_5 or a derivative thereof) may be divided into the following classes, the existence of which is largely dependent on the chemical character of the group X :

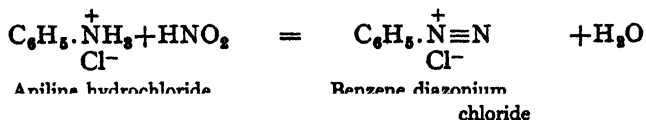
- (a) Compounds of the structure $\text{Ar} \cdot \overset{+}{\text{N}} \text{:} \ddot{\text{N}} \text{X}^-$, such as the *diazonium salts*, e.g. $\text{C}_6\text{H}_5\text{N}_2\text{Cl}$, which resemble ammonium salts in character.
- (b) Compounds of the structure $\text{Ar} \cdot \text{N} \text{:} \text{N} \cdot \text{X}$. These are *diazo-compounds* comparable to the azo-derivatives, and sometimes occur in two stereoisomeric forms, viz. :

1. *Syn-diazo-compounds* of the type $\begin{array}{c} \text{Ar} \cdot \text{N} \\ \text{X} \cdot \ddot{\text{N}} \end{array}$, which are produced in the first instance, but owing to their extremely labile nature have only been isolated in a few cases.
2. *Stable anti-diazo-compounds* of the structure $\begin{array}{c} \text{Ar} \cdot \text{N} \\ \ddot{\text{N}} \cdot \text{X} \end{array}$.

The diazonium salts are by far the most important of the above derivatives and will therefore be treated in most detail.

1. Diazonium Salts

Preparation.—If the diazonium salts are only required in solution, their preparation is exceedingly simple. A well-cooled aqueous solution of a salt of a primary aromatic amine, containing at least one equivalent of free mineral acid, is treated with the calculated amount of sodium nitrite dissolved in water. Free nitrous acid is liberated, and *diazotisation* proceeds as in the following equation :

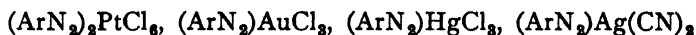


The resulting diazonium salt remains in solution and may be employed directly for the production of other compounds, such as azo-dyes. This method of diazotisation is carried out on a very large scale industrially.

¹ See *The Aromatic Diazocompounds*, by K. H. Saunders (Arnold), 1949.

Owing to the high solubility of most of the diazonium salts in water, and the ease with which they undergo decomposition, a different method has to be adopted for the preparation of the salts in the solid state. For this purpose an alcoholic solution of the amine is treated with the requisite acid, and amyl nitrite added to the cooled mixture. The salt either separates out immediately or is thrown out by the addition of ether. Generally it is even more convenient to diazotise in glacial acetic acid solution. It is only in rare instances that the diazonium salt requires to be isolated in the pure state in this manner.

Properties.—Diazonium salts are usually colourless crystalline substances, which are readily soluble in water, less soluble in alcohol, and in the dry state explode violently when heated or struck. In every respect they are genuine salts, comparable to the ammonium and especially to the quaternary ammonium salts. Diazonium nitrates and chlorides are neutral in aqueous solution, and the conductivity figures show them to be ionised to about the same extent as the corresponding potassium and ammonium salts. The resemblance to ammonium salts is also exhibited in the formation and character of complex compounds, such as chloroplatinates, aurochlorides, mercury double salts and diazonium silver cyanides :

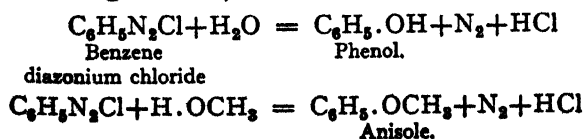


Diazonium hydroxides, $\text{ArN}_2.\text{OH}$, have been obtained in solution only, by treating the diazonium chlorides with silver oxide or the sulphates with barium hydroxide. They are very unstable substances, which are proved to be genuine hydroxyl bases by their conductivity and the speed with which they bring about hydrolysis. In this respect their strength varies between that of ammonia and that of the alkali hydroxides.

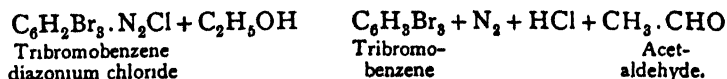
Reactions of the Diazonium Salts

These reactions are used in the preparation of a great variety of benzene derivatives. Many of them depend on the ease with which diazonium salts, or the neutral diazo-compounds with which they are in equilibrium, decompose with *elimination of nitrogen*, the place of which is then taken by other atoms or groups. It is believed that this decomposition results in the liberation of a highly reactive *aryl radical*, e.g. phenyl, C_6H_5 , which rapidly attacks any molecule in its neighbourhood. For further details see p. 483.

(1) *Replacement of N_2 -group by hydroxy-, alkoxy-, or acyloxy-groups.* The interaction of diazonium salts with hydroxy-compounds—on warming with water, alcohol, or acetic acid—leads to the formation of phenol or its derivatives as the chief product of reaction, and may be formulated in the case of benzene diazonium chloride in the following manner (intermediate phases being omitted) :

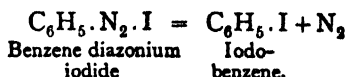


(2) *Replacement of the N_2 -group by hydrogen* occurs as a by-reaction in the above decomposition with alcohol. In the case of negatively substituted diazonium salts this becomes the main reaction. Tribromobenzene diazonium salts, for example, yield almost exclusively tribromobenzene, even with very dilute aqueous alcohol.

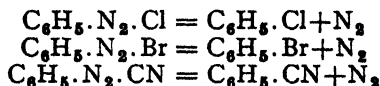


Other reducing agents, such as alkaline stannous chloride solution, also replace the nitrogen group by hydrogen.

(3) *Replacement of the N_2 -group by iodine* occurs on merely warming a solution of a diazonium iodide. The reaction is often employed as a preparative method, since many iodo-compounds are thus obtained in good yield.



(4) *Replacement of the N_2 -group by halogeno or cyano groups.* It is not possible to introduce these substituents into the benzene ring in the manner described under (3) above. Sandmeyer, however, discovered that the change could be effected with the aid of the corresponding cuprous salts. When solutions of the diazonium salts are heated in the presence of cuprous chloride, bromide, or cyanide, there are formed chloro-, bromo-, or cyanobenzenes (*Sandmeyer reaction*).



The Sandmeyer reactions depend in part on the union of the diazo-compound with cuprous salts to form double compounds, which are very easily decomposed.

A modification of the above is the *Gattermann reaction*. The cuprous salts are here replaced by copper powder, which in the main appears to act catalytically.

Diazonium borofluorides decompose on warming to form the corresponding aryl fluoro-compounds,¹ $\text{Ar} \cdot \text{N}_2 \cdot (\text{BF}_4) \longrightarrow \text{Ar} \cdot \text{F} + \text{N}_2 + \text{BF}_3$.

(5) *Replacement of the N_2 -group by the nitro group.* Several methods are available for the preparation of nitro-compounds from aromatic amines. The yields are generally poor, but a promising method is that of Hodgson and Marsden² in which aryl diazonium cobaltinitrites are treated with cuprous oxide and cupric sulphate.

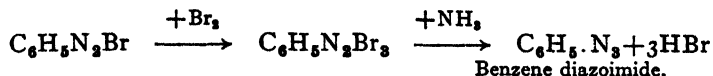
As diazonium salts are readily prepared from nitro-compounds by way of the amines, the reactions just described are frequently employed

¹ G. Balz and G. Schiemann, *Ber.*, 1927, 60, 1186. ² H. H. Hodgson and E. Marsden, *J.*, 1944, 22.

in the laboratory for converting aromatic nitro-compounds into the corresponding hydroxy-, chloro-, bromo-, cyano- and other derivatives. Nitro-compounds thus form a valuable means of passing from an aromatic compound to its various derivatives.

In addition to these remarkable reactions of the diazonium salts, there are also other important changes which proceed *without elimination of nitrogen*.

(1) Diazonium bromides add on bromine to form perbromides, and these by treatment with ammonia yield diazoimides, which may be regarded as derivatives of hydrazoic acid.

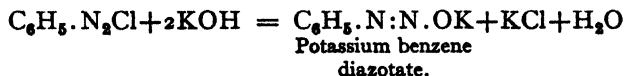


(2) On reduction, diazonium salts are converted into monosubstituted hydrazines (see p. 485).

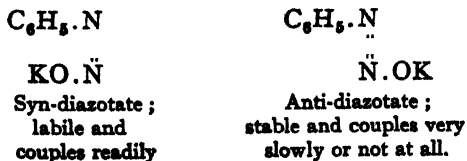
(3) Reactions of the highest importance are those which lead to the *production of azo-dyes from diazonium salts*, by the "coupling" of the latter with amines and phenols. These are dealt with under the heading of azo-dyes (p. 490).

2. Diazo-Compounds, $\text{Ar}\cdot\text{N}:\text{NX}$

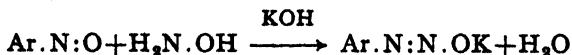
When a diazonium salt is treated with alkalis it is converted into a metallic salt or diazotate of the formula $\text{Ar}\cdot\text{N}_2\cdot\text{OM}$, in which the diazo-hydroxide plays the part of an acid *e.g.*,



These diazotates can exist in two isomeric modifications, which are colourless and possess many properties in common. Both are readily reduced to hydrazines, and with benzoyl chloride yield nitrosobenzanilides. On oxidation both are converted into nitramine salts, *e.g.* $\text{Ar}\cdot\text{N}_2\text{O}\cdot\text{ONa}$. They differ mainly in the relative speeds with which they undergo reaction. For example, the labile diazotates first formed couple with phenols in alkaline solution to give azo-dyes, whereas the stable diazotates obtained by the more prolonged action of alkalis on diazonium salts either fail to give this reaction or react very slowly. With mineral acids the diazotates are transformed back into diazonium salts. These diazotates are structurally similar and their differences are regarded as due to stereoisomerism (Hantzsch), as illustrated in the following formulæ :

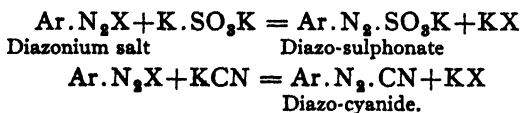


According to this view both *syn*- and *anti-diazohydroxides* are to be regarded as stereoisomeric oximes of nitrosobenzene. Experiment has shown that both forms are actually produced by the interaction of hydroxylamine and nitrosobenzene.



In this reaction labile *syn*-forms are first obtained, which then pass into the stable *anti*-modifications.

Stereoisomerism of a similar type has also been found to exist in the case of the diazo-sulphonates, $\text{Ar.N:N.SO}_3\text{K}$, and the diazo-cyanides, Ar.N:N.CN . These are obtained from diazonium salts by the action of potassium sulphite and potassium cyanide respectively.



The stable *anti*-diazocyanides are converted into the labile and reactive *syn*-forms by exposure to light.¹ Confirmation of the conclusion of Hantzsch that the stable compounds are of the *anti*-configuration has now been obtained by dipole moment determinations, the values being small compared with those of the *syn*-forms.²

Opposed to the views of Hantzsch are those of Hodgson³ who maintains that the diazosulphonates and cyanides are *structural* isomers and not *geometrical* isomers. Careful investigations by means of infra-red spectra, etc., however, lend little support to Hodgson's standpoint.⁴

When diazonium chloride solutions are treated with a small excess of silver oxide there are obtained solutions of the very unstable diazonium hydroxides, *e.g.* $\text{C}_6\text{H}_5\text{N}_2\text{OH}$. The normal (*syn*-) metallic diazotates on careful addition of acetic acid do not yield the hydrates, but deposit the corresponding *diazooanhydrides* (*diazo-oxides*).

Relationship between Nitrosamines and Diazo-Compounds

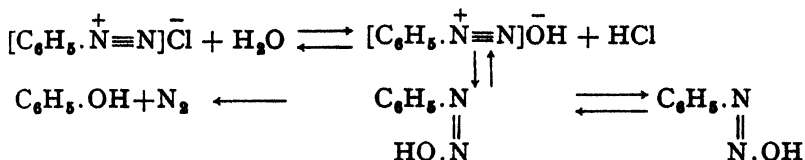
Primary Nitrosamines and Anti-diazohydroxides.—The group $\text{—N}_2\text{OH}$ in the compounds $\text{R.N}_2\text{OH}$ is tautomeric, functioning either as an *anti*-diazohydroxide (—N:N.OH) or as a primary nitrosamine structure (—NH.NO). According to the researches of Hantzsch and his co-workers, all the metallic salts, $\text{R.N}_2\text{OM}$, are to be regarded as *anti*-diazotates, but the free hydrogen derivatives may exist either as diazohydrates, R.N:N.OH , or, as more frequently happens, as primary nitrosamines, R.NH.NO . Hence, in the latter case, during the conversion of the salt (diazotate) into the hydrogen compound, an intramolecular rearrangement takes place, $\text{Ar.N:N.OK} \longrightarrow \text{Ar.NH.NO}$. Conversely, the primary phenyl nitrosamines behave as pseudo-acids, reacting with alkalis to form salts of the *anti*-diazohydrate structure. The *anti*-diazotates are thus closely related to the nitrosamines.

¹ O. Stephenson and W. A. Waters, *J.*, 1939, 1796. ² R. J. W. Le Fevre and H. Vine, *J.*, 1938, 41. ³ H. H. Hodgson, *J.*, 1943, 470; 1944, 395. ⁴ D. Anderson, R. J. W. Le Fevre and J. Savage, *J.*, 1947, 445. H. Sheppard and G. B. B. M. Sutherland, *J.*, 1947, 453. H. C. Freeman and R. J. W. Le Fevre, *J.*, 1951, 415. N. Campbell, A. W. Henderson and D. Taylor, *J.*, 1953, 1281.

The isolation of both isomeric forms of the hydrogen compound from one and the same tautomeric substance has been effected in a few instances, *e.g.* in the case of 2:4:6-tribromobenzene anti-diazo-hydrate, $C_6H_3Br_3.N:N.OH$, and the corresponding nitrosamine, $C_6H_3Br_3.NH.NO$. These isomerides recall the somewhat similar aliphatic nitroso-compounds, $R_2CH.NO$ and $R_2C:N.OH$, and their formation is analogous to that of the isomeric nitro-compounds (p. 173). In chemical behaviour the isomerides differ in accordance with the formulæ given above. The anti-diazo-hydrates resemble reactive hydroxy acids, whereas the nitrosamines are indifferent pseudo-acids.

Homolytic Reactions of Diazonium Salts and Diazocompounds¹

Hantzsch assumed that the decomposition of a diazonium salt in water was dependent on its partial hydrolysis to form the diazonium hydroxide, which then entered into equilibrium with the isomeric *syn*- and *anti*-diazohydroxides. Of these, the *syn*-diazohydroxide was supposed to be highly unstable, rapidly breaking down to give a phenol and nitrogen.



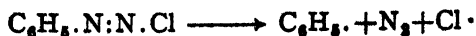
In the presence of an alcohol the reactive *syn*-diazohydroxide was represented as combining with the alcohol to form an addition compound, which then disrupted to yield a hydrocarbon, alkoxy-derivative or other product.

These views have recently been modified and extended by later discoveries. Benzene diazonium chloride has long been known to react with methyl and ethyl alcohols, for example, the main changes being expressed as follows :



But despite the striking dissimilarity of these processes, the two reactions have been found to occur with the same velocity³ as measured by the rate of evolution of nitrogen. Higher alcohols also react with the same velocity as methyl and ethyl alcohols. It is very unlikely that the intermediate products required by the above mechanism of Hantzsch would all decompose at the same rate, and a new explanation has now been advanced which links up the reactions of diazonium salts and diazo-compounds with those of the nitrosoacylarylamines, *e.g.* nitrosoacetanilide, $C_6H_5.N(NO).COCH_3$.

According to modern views, the diazonium salt, or more probably its covalent tautomer (*e.g.* $C_6H_5 \cdot N:N \cdot X$), slowly breaks down with loss of nitrogen and liberation of a free phenyl or other aryl radical. The latter



¹ For further details see D. H. Hey and W. A. Waters, *Chem. Rev.*, 1937, **21**, 169.
² Pray, *J. Phys. Chem.*, 1926, 1477.

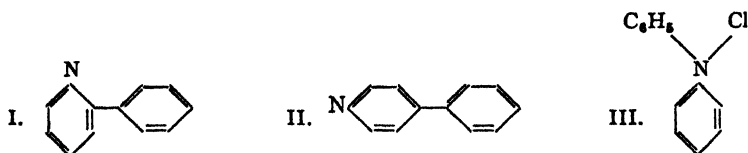
is exceedingly reactive and immediately attacks any molecule in its neighbourhood. The part of the change which determines the observed rate of reaction is therefore the *slow* decomposition of the diazo-compound, which is a unimolecular reaction and largely independent of the medium in which it occurs.

Waters¹ allowed dry benzene diazonium chloride to decompose under acetone and showed that benzene and chloroacetone were formed. The

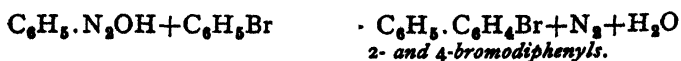


phenyl radical on being set free immediately attacks the acetone, removing hydrogen to give benzene. The production of chloroacetone indicates the liberation of a neutral active form of chlorine, since the chlorine anion is stable and non-reactive.

Liberation of active chlorine was also proved by adding metals such as Sb, Bi, Pb and Hg, when these were also attacked and converted into chlorides (even in the presence of excess calcium carbonate, which would have neutralised any hydrogen chloride). It is therefore concluded that phenyl diazonium chloride decomposes into the neutral products, $\text{C}_6\text{H}_5\cdot$, $\text{Cl}\cdot$ and N_2 . Further confirmation of the neutrality of the disruption products is afforded by the interaction of aqueous solutions of diazonium salts with an excess of pyridine² to form α -, β -, and γ -arylpiperidines. If the diazonium salt reacted as such it would be expected to break down into a positively charged phenyl ion and negatively charged chloride which would combine with pyridine to form the quaternary salt III, or by a subsequent migration α - and γ -arylpiperidines (I and II) only.



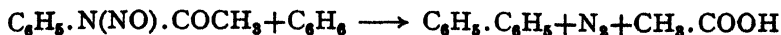
Another set of reactions which is believed to be dependent on the formation of free radicals is the decomposition of diazohydroxides in the presence of aromatic liquids. Gomberg diazotised aromatic amines, using the minimum amount of water, and added benzene or another aromatic liquid followed by a 20 per cent. solution of sodium hydroxide. Rapid reaction set in, which led to the formation of a diaryl, *e.g.*



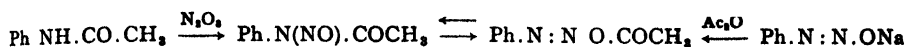
This change is also more readily explained on the assumption that free phenyl radicals are liberated by the disruption of the diazohydroxide. A curious feature is that the usual laws of benzene substitution do not hold for the reactions with free radicals (see p. 446).

¹ W. A. Waters, *J.*, 1937, 113, 2007, 2014. ² J. W. Haworth, I. M. Heilbron and D. H. Hey, *J.*, 1940, 349.

Similar results have been obtained in the decomposition of nitroso-acylarylamines. For example, nitrosoacetanilide (prepared by the action of N_2O_3 on acetanilide dissolved in acetic acid) reacts with benzene to form diphenyl (*Bamberger*).

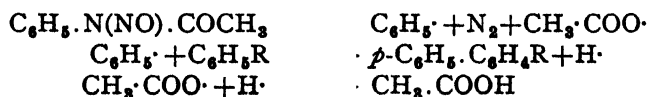


It was shown by Bamberger, Hantzsch and others that nitrosoacetanilide is tautomeric with benzene anti-diazoacetate, because the compound obtained by the action of N_2O_3 on acetanilide is the same as that produced by the acetylation of sodium benzene diazohydroxide :



It would therefore not be unexpected if the reactions undergone by nitrosoacetanilide (benzene diazoacetate) resembled those given above for the diazohydroxides.

Proof that the reactions are the same was provided by Grieve and Hey.¹ The nitroso compound has been shown to interact with toluene, chlorobenzene, nitrobenzene and benzaldehyde to give the corresponding diphenyls. Moreover, these changes all proceed with the same velocity, despite the different nature of the substituent groups present. The reaction is therefore expressed as follows :



Although the free phenyl radical thus displaces hydrogen in an *aromatic* ring to form a diaryl, the reaction with an *aliphatic* organic compound takes place in a different manner. Waters found that dry nitrosoacetanilide decomposes in the presence of hexane, cyclohexane, ether, dioxan, acetone, ethyl acetate or acetic anhydride with the production of benzene ($C_6H_5\cdot + RH \longrightarrow C_6H_6$, compare reaction of benzene diazonium chloride with ethyl alcohol). On the other hand, aliphatic halogen derivatives such as alkyl halides, chloroform or carbon tetrachloride are attacked with the formation of a halogenated benzene ($C_6H_5\cdot + C_2H_5Br \longrightarrow C_6H_5Br$).

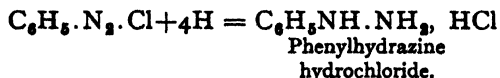
Hydrazines

Aromatic hydrazines are classified in the same manner as the aliphatic compounds. Symmetrical disubstituted aromatic hydrazines, usually termed hydrazo-compounds, have already been dealt with on p. 477.

¹ *J.*, 1934, 1797.

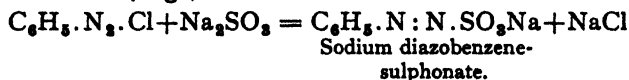
The *monosubstituted hydrazines*, of which phenylhydrazine, $\text{C}_6\text{H}_5\text{.NH.NH}_2$, is the best known example, are the most important. These are generally prepared by the reduction of the corresponding diazonium salts, which may be effected in two ways :—

(a) By treating diazonium salts with stannous chloride in hydrochloric acid solution.

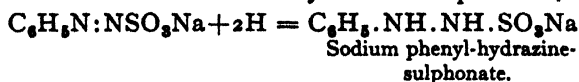


Substituted phenylhydrazines such as chloro- and bromo-phenylhydrazines are best prepared in this way. In such cases the amines are diazotised in presence of a great excess of acid ; otherwise, undesirable by-products are obtained.¹

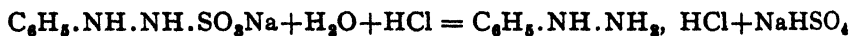
(b) According to the older method of Emil Fischer, by which phenylhydrazine was first discovered. The solution of a diazonium salt is allowed to react with neutral sodium sulphite, whereby a diazo-sulphonate (see p. 482) is formed, *e.g.*,



On reduction with sulphurous acid, or zinc dust and acetic acid, the diazo-sulphonate is converted into a hydrazine-sulphonate,



When this is heated with hydrochloric acid the sulphonic group is removed and phenylhydrazine hydrochloride obtained.



In each of the above methods an amine forms the starting-point, and it is converted into the diazonium salt, and finally into the hydrazine, without actually isolating any of the intermediate products.

The monosubstituted hydrazines are monacid bases, which distil without decomposition under diminished pressure. They are sparingly soluble in water, readily soluble in alcohol and ether, and reduce Fehling's solution.

Phenylhydrazine, $\text{C}_6\text{H}_5\text{.NH.NH}_2$, is prepared on the large scale according to method (b) described above. It is a colourless liquid which boils with slight decomposition at 241° , under atmospheric pressure. On cooling it solidifies to large colourless prisms, m.p. 19.6° . The hydrochloride crystallises in white leaflets, which are not very soluble in cold water, and dissolve very sparingly in concentrated hydrochloric acid.

As has already been mentioned, phenylhydrazine is a valuable reagent for identifying aldehydes and ketones, and has proved of special service in the investigation of the sugars (see p. 304, *et seq.*). It is a strong reducing agent, and precipitates cuprous oxide from Fehling's solution ;

¹ B. M. Barclay and N. Campbell, *J.*, 1945, 530.

in such reactions the phenylhydrazine decomposes into benzene, nitrogen and hydrogen.

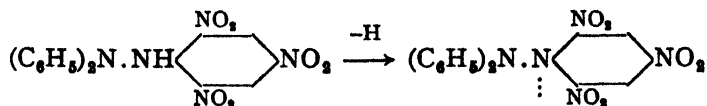


When treated with energetic reducing agents it yields aniline and ammonia, $\text{C}_6\text{H}_5\cdot\text{NH}\cdot\text{NH}_2 + 2\text{H} = \text{C}_6\text{H}_5\cdot\text{NH}_2 + \text{NH}_3$. Phenylhydrazine unites with β -diketones and β -ketonic esters to form derivatives of pyrazole and pyrazolone respectively. Acetoacetic ester, for example, gives phenyl-methyl-pyrazolone, which on methylation is converted into antipyrine, a substance extensively used in medicine as a febrifuge.

2 : 4-Dinitrophenylhydrazine is now used extensively for the identification of aldehydes and ketones since it gives 2 : 4-dinitrophenylhydrazones which crystallise beautifully and have convenient melting-points. It is readily prepared by the interaction of 1-chloro-2 : 4-dinitrobenzene with hydrazine.

The behaviour of **tetraphenylhydrazine** in dissociating in solution into *nitrogen diphenyl* has already been discussed on p. 475. Hexaphenyl ethane decomposes in a similar manner to form triphenylmethyl (p. 561).

Reference has also been made to the dissociation of **hexaphenyl-tetrazane** into two molecules of *triphenyl-hydrazyl* (p. 475). In the solid state hexaphenyl-tetrazane is colourless ; in solution at 0° it is deep blue, although the blue triphenyl-hydrazyl is extremely unstable. A more stable divalent nitrogen derivative may be obtained from *aa-diphenyl- β -trinitrophenylhydrazine*, a yellowish-red crystalline substance, which when oxidised in benzene or chloroform solution with lead dioxide yields the monomolecular *aa-diphenyl- β -trinitrophenylhydrazyl*. The latter forms violet black crystals, soluble in organic solvents to give deep violet solutions. In the above reaction the hydrazine is converted into the completely monomolecular hydrazyl.



This compound is the analogue of tribiphenylmethyl (described later) and is distinguished from other derivatives of divalent nitrogen by its great stability.

VI.—AZO-DYES

Dyeing¹

The dyeing of spun threads may be mechanical or chemical. In the former case, which does not further concern us, a coloured precipitate (pigment) is produced on the threads, or the latter are coated with a thin layer of a coloured substance. Of much greater interest is chemical

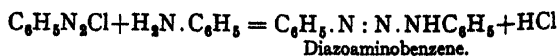
¹ See *The Synthetic Dyestuffs*, by J. C. Cain and J. F. Thorpe, (Griffin); *Fundamental Processes of Dye Chemistry*, by H. E. Fierz-David and L. Blangey (Interscience Publishers, Inc.); *Synthetic Colouring Matters, Vat Colours*, J. F. Thorpe and C. K. Ingold (Longmans); *The Development of the Chemistry of Commercial Synthetic Dyes* (1856-1938) (Institute of Chemistry, 1938), F. M. Rowe.

dyeing, in which the fabric is usually immersed in a hot aqueous solution of the dye, removing the latter from the solution and becoming thereby coloured. No satisfactory explanation can at present be advanced which will cover all the different processes of chemical dyeing. The majority of chemists assume that in many cases, at all events, dyeing is dependent on a kind of salt formation between the dye and the constituents of the thread, an assumption supported by the fact that a dye always possesses basic or acidic character. Probably the dye is bound to the animal fibre by the amino-, carboxyl and acid amide groups present in the surface of the threads. It must be emphasised that a characteristic difference is shown between yarns of animal (wool, silk) and those of vegetable origin (cotton, artificial silk). Most dyes colour the former directly (**substantive** or **direct dyeing**) but are not capable of dyeing vegetable threads without special treatment. It is, however, possible to fix the colour to the latter if the fabric is previously impregnated with certain substances which will unite with the dye (**mordant dyeing**). Substances of this type are termed **mordants**. In working with basic dyes, mordants such as tannin are employed, which combine with the dye to form insoluble salts, *e.g.* of tannic acid. In most cases the process is completed by treatment with a solution of potassium antimonyl tartrate. With acid dye-stuffs, on the other hand, cotton requires to be impregnated with a basic mordant such as aluminium, iron or chromium hydroxide. The fabric is steeped in an aqueous solution of the metallic acetate and then heated in steam, whereby the acetate is decomposed with the production of the corresponding hydroxide. Acid dyes combine with these hydroxides to form insoluble **lakes**. As will be seen later, alizarin dyes are commonly employed in this manner. Dye-stuffs are also known which are capable of colouring cotton directly or substantively, *i.e.* without the addition of mordants, in the same way as the wool dyes affix themselves to wool. Chief among this class are azo-dyes obtained from benzidine, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{NH}_2$, and its derivatives, which contain two of the chromophore groups $-\text{N} : \text{N}-$. These are distinguished from monoazo-dyes by the term **disazo-dyes**.

General Methods of Formation

It has already been remarked (see p. 481) that diazo-compounds "couple" with amines and phenols with great readiness to form azo-dyes. Although this process is formulated in the following pages as a simple change, it is in all probability one of some complexity.

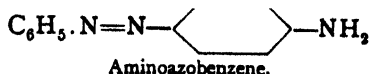
(a) Equimolecular quantities of diazonium salts and *primary* or *secondary* aromatic amines react together to form *diazoamino-compounds*, *e.g.*



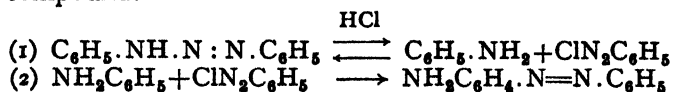
The most interesting property of these compounds is their transformation into the structurally isomeric **aminoazo-compounds**. In the case of diazoaminobenzene this change can be effected by merely allowing the substance

$$\text{C}_6\text{H}_5 \cdot \text{N}=\text{N}-\text{NH}-\langle$$

Diazoaminobenzene

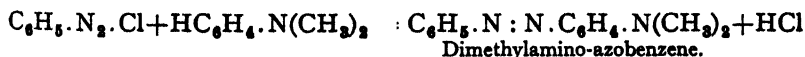


The diazoaminobenzene-aminoazobenzene isomerisation seems to be *intermolecular* and occurs in two stages: (1) a reversible fission under the influence of hydrochloric acid to give the amine and free diazobenzene chloride; (2) an irreversible interaction of these products to give the aminoazo compound.

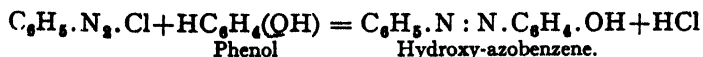


Aminoazobenzene is the parent substance of a large number of azo-dyes.

(b) Diazonium salts and *tertiary* aromatic amines react directly with each other to form aminoazo-compounds.



(c) In a similar manner phenols unite with diazonium salts in the presence of alkalis to form hydroxyazo-compounds :



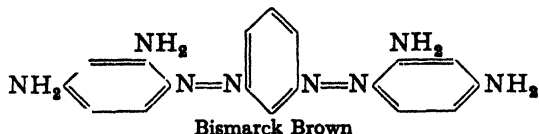
Here also it has been found that only those hydrogen atoms in the *o*- or *p*-positions to the phenolic hydroxy-group are capable of entering into reaction. If hydrogen is only available in the *m*-position, no coupling takes place unless the substituents in the reactive positions are particularly easily detached.

The instances already quoted are simple examples of the typical reactions by which the great majority of the monoazo-dyes are prepared. It is readily understood that these reactions are influenced by the specific constitution of both reagents, and that the velocity of coupling depends on the structure of the amines and phenols, as well as on that of the diazo-compound employed.

Azo-compounds as Dyes

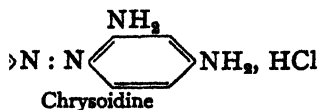
The azo-dyestuffs form one of the most important groups of dye-stuffs. Not only do they constitute more than half the number of marketed synthetic dyes, but they provide a remarkable range of shades and colours for a great variety of purposes such as dyeing wool, silk, cotton, linen, leather, etc. Many are very fast to light and washing. The majority are acidic as they contain the sulphonic acid group, but some are basic with amino-groups in the molecule.

The first azo-dye to be sold in England was **Aniline Yellow** (aminoazobenzene) which appeared on the market in 1863, although Peter Griess had obtained it four years earlier by the rearrangement of diazoaminobenzene. In 1863 Martius discovered **Bismarck Brown**, which was manufactured in 1865. It is prepared by the action of nitrous acid on *m*-phenylene diamine, and is a mixture, the chief constituent being the hydrochloride of the following bisazo-compound.

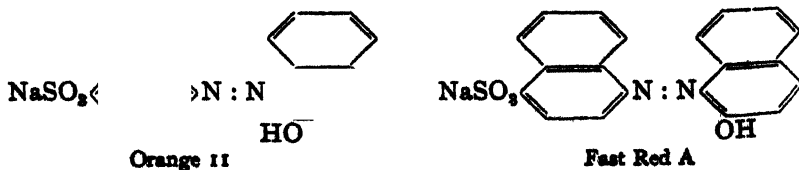


Bismarck Brown is an example of a basic azo-dye. It is used for dyeing wool and leather goods, but can be applied to cotton only on a tannin mordant.

The tremendous development of the azo-dyestuff industry, however, is based not on these early isolated examples, but on the work of Peter Griess, who, as already mentioned, obtained the diazo compounds and applied his discovery to the manufacture of azo-dyestuffs by the "coupling" reaction already mentioned in which diazonium compounds are condensed with phenols or amines. The first industrial application was the manufacture of **chrysoidine** discovered independently by Caro (1875) and Witt (1876). It is a basic azo dye, prepared by the interaction of benzene diazonium chloride on *m*-phenylenediamine. It is used with a tannin mordant for dyeing cotton.



The first commercial acidic azo-dyes (1876) were **Orange I** and **Orange II**, prepared by coupling diazotised sulphanilic acid with α - and β -naphthol respectively. The second dyestuff, also known as

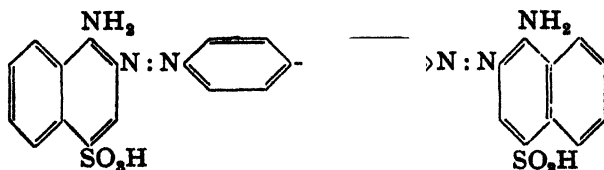


Naphthalene Orange G, is used for dyeing wool and silk as well as leather and paper. The sulphonic acid group is present in the majority of azo-dyes since without affecting the colour it renders the dye water-soluble and direct to wool and silk. A dye similar in structure and mode of preparation is **Fast Red A**, the first azo red dye and also the first dye made entirely from naphthalene derivatives. The deepening of the colour compared to Orange 11 is typical of the effect obtained by replacing a benzene nucleus by a naphthalene nucleus.

It is of interest to note that the discovery that naphthalene derivatives give good dyes led to intensive investigation which added greatly to our knowledge of naphthalene chemistry.

An azo dye frequently encountered in the laboratory is **helianthine** or **methyl orange** produced by the action of dimethylaniline on a diazotised solution of sodium sulphanilate. It is largely used as an indicator in volumetric analysis, the yellow colour of the aqueous solution changing to red on acidification. Instead of a full graphic formula azo dyes are frequently described by giving the names of the constituents separated by an arrow to represent the coupling. For example, methyl orange is represented by sulphanilic acid \rightarrow dimethylaniline, which is a short-hand way of stating that methyl orange is formed by the coupling of diazotised sulphanilic acid with dimethylaniline.

The first azo dyes could be applied directly from aqueous solution to animal fibres such as wool and silk, but not directly to cotton. A few basic dyes such as Bismarck Brown could be used for dyeing cotton, but only when the fabric was first mordanted with tannin. In 1884 a notable advance was made when Griess found that certain disazo dyes derived from benzidine could dye cotton without a mordant. These dyes, however, were not completely satisfactory, and it was left to Böttiger to produce in the same year **Congo Red** the first dye substantive to cotton. This dye is prepared by tetrazotising benzidine and coupling it with two molecules of naphthionic acid. In spite of its sensitiveness to acids, it is still much used in dyeing.



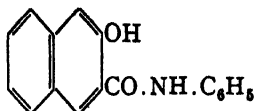
Congo Red

By employing various substituted benzidines and *p*-phenylenediamines a great range of direct cotton colours has been obtained.

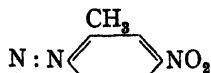
The azo-dyes we have been considering are water-soluble, but it is possible to apply to the fibre insoluble or slightly soluble dyestuffs by preparing them *in-the fibre*. Two methods are used.

In 1880 Holliday succeeded in impregnating cotton with β -naphthol in alkaline solution and then treating it with diazotised *p*-nitraniline.

Para Red (*p*-nitraniline \rightarrow β -naphthol) thus formed in the fibre is an insoluble pigment and a representative of the class of dyes known as **Ice Colours** or **Azoic Colours**, the first name owing its origin to the ice employed in preparing the diazonium compound. The importance of this type of dye, however, is due to the discovery of **Naphthol AS** or the anilide of 2-hydroxy-3-naphthoic acid and similar compounds which unlike β -naphthol possess considerable affinity for the cotton fibre and give rise to a great number of different colours. The value of the method has been greatly enhanced by the production of stabilised diazo- $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{N} \parallel \text{N} \cdot \text{ONa}$ compounds which can be transported and stored safely and used when wanted. **Nitrosamine Red** the sodium *anti*-diazotate of *p*-nitraniline has long been known. Stabilisation may be effected in other ways such as formation of the double salts with zinc chloride, etc. The first commercial Naphthol AS dye was **Griesheim Red** obtained by coupling diazotised 2-methyl-4-nitroaniline with Naphthol AS.



Naphthol AS



Griesheim Red

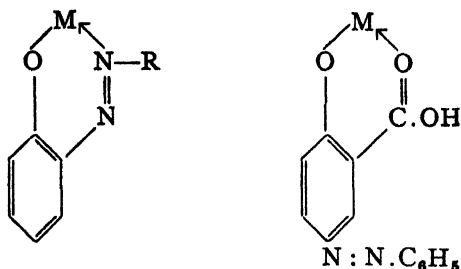
The reverse method of preparing a dye in the fibre was due to A. G. Green's discovery in 1887 that **primuline**, a direct cotton dye previously prepared by him, could be diazotised in the fibre and then coupled with a second component such as β -naphthol. These are early examples of **Ingrain** or **Developing Dyes**, and their formation shows how only slightly soluble dyes may be applied to the fibre.

There is yet another method of preparing dyes in or on the fibre which is fundamentally different from those just discussed. It is possible to precipitate on a textile a substance known as a **mordant** which not only adheres to the fibre but can at the same time combine with a dye to form an insoluble coloured **lake**. These lakes thus impart a permanent colour to the fibre. We may define mordants as substances which can unite with certain dyestuffs to form insoluble coloured compounds (lakes) which are permanently fixed on the fibre.

Mordants are of two types.

- (a) **Acid mordants**.—These are of minor importance. Certain basic azo-dyes can dye cotton if tannic acid is used as a mordant.
- (b) **Metallic mordants**.—These are the oxides or hydroxides mainly of chromium, iron, aluminium, copper, or tin. Iron and copper give the most permanent lakes, and aluminium and tin the brightest. Chromium is most generally used.

Considerable study has been done on the structure of lakes, one of the main properties of which is that the metal is not present as a simple

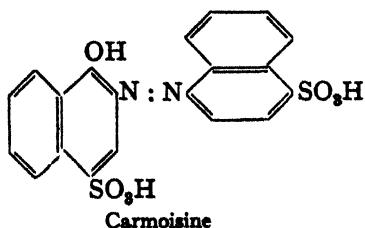


ion. Werner was the first to point out that mordants function by forming co-ordinated ring compounds, and striking confirmation of this comes from a survey of the constitution of the azo mordant dyes. For the formation of a chrome lake it appears that these dyes require a hydroxyl group *ortho* to another hydroxyl, carboxyl, or azo group. Formation of five- or six-membered rings then occurs by the installation of a co-ordinate link between the metal and an oxygen or nitrogen atom as in the above formulæ. The structures are not so simple as represented above and probably involve resonating formulæ (see, for example, p. 598). The main point, however, is that lakes contain stable co-ordinated five- or six-membered rings of the above type.

Mordanting finds its biggest application in woollen dyeing and some of the fastest azo-dyes are formed from chromium or copper mordants. The former is generally prepared by soaking the wool in a solution of sodium or potassium dichromate and then treating it with lactic or tartaric acid.

Cotton mordanting is more difficult owing to the small affinity of metallic salts, hydroxides, and oxides for cotton fibre. The cloth is soaked in a solution of the acetate of chromium, iron, or aluminium and then heated in a moist atmosphere. A fine precipitate of the metallic oxide is thus formed on the fibre and is then "fixed" by treatment with chemicals such as the phosphates or carbonates of potassium, sodium, or calcium.

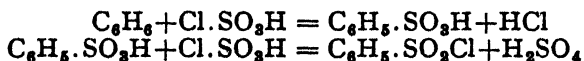
An example of an azo mordant dye is **Carmoisine**, made by coupling naphthionic acid with α -naphthol-4-sulphonic acid. It is used not only as a red acid dye, but also for the production of violet-blue shades with a chromium mordant.



VII

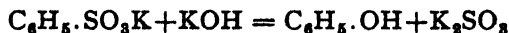
Aromatic Sulphonic Acids

Formation.—When aromatic hydrocarbons or their derivatives are treated with sulphuric acid they yield sulphonic acids, in which hydrogen of the benzene nucleus is replaced by the sulphonic group SO_3H , *e.g.* $\text{C}_6\text{H}_6 + \text{H}_2\text{SO}_4 = \text{C}_6\text{H}_5\cdot\text{SO}_3\text{H} + \text{H}_2\text{O}$. *Sulphonation* is effected by the use of ordinary sulphuric acid, or of fuming acid containing varying proportions of anhydride, the temperature being regulated according to the ease with which the reaction occurs. In this way, by choosing the conditions, it is possible to prepare mono- or polysulphonic acids. Chlorosulphonic acid is also a useful sulphonating agent. Considerable quantities of sulphonyl chlorides are often obtained when this reagent is used, doubtless due to its action on the sulphonic acid first formed.¹



In the case of benzene a maximum of three sulphonic groups may thus be introduced into the molecule. The sulphonic acids either separate directly from the acid mixture on cooling, or are precipitated in the form of their alkali salts by the addition of salt, sodium acetate or potassium chloride. They may also be separated from the excess of sulphuric acid as the soluble calcium, barium or lead salts.

Properties and Chemical Behaviour.—The sulphonic derivatives of the hydrocarbons are all readily soluble in water, and form more or less easily crystallisable substances of strongly acidic character. By the action of superheated steam, or of concentrated hydrochloric acid at 150° , they may be converted into the original hydrocarbons (see p. 455). When fused with alkalis they yield phenols, a reaction which is of great importance technically.

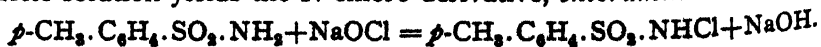


On being heated with potassium cyanide the salts of sulphonic acids pass into the corresponding nitriles, which may be hydrolysed to carboxylic acids.



The alkali salts of the sulphonic acids with phosphorus pentachloride yield *sulphonyl chlorides* of the formula $\text{R}\cdot\text{SO}_2\cdot\text{Cl}$. With ammonia or ammonium carbonate, these give crystalline *sulphonamides*, $\text{R}\cdot\text{SO}_2\cdot\text{NH}_2$. The latter are frequently used in the identification of the sulphonic acids.

Related to the sulphonamides are the chloramides, of which two are particularly well-known. *p*-Toluenesulphonamide with sodium hypochlorite solution yields the N-chloro-derivative, *chloramine T*.



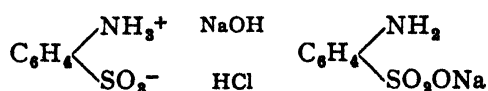
¹ Harding, *J.*, 1921, 229, 1261.

This substance with water slowly liberates hypochlorous acid and is a useful antiseptic. It is used in the form of the sodium salt, R.NaCl . Further treatment with hypochlorous acid gives the dichloro-product, *dichloramine T*, $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\cdot\text{NCl}_2$, which is a good disinfectant. If the methyl group is replaced by the carboxyl group *halazone* is obtained and is used for sterilising drinking water.

Benzene sulphonic acid, $\text{C}_6\text{H}_5\cdot\text{SO}_3\text{H}$, crystallises in plates, m.p. 66° , which very readily dissolve in water. Its chloride may be used for distinguishing between primary and secondary amines (p. 179).—**Benzene disulphonic acids**, $\text{C}_6\text{H}_4(\text{SO}_3\text{H})_2$. When benzene is heated with fuming sulphuric acid, a mixture of the *m*-disulphonic acid, m.p. 63° , with a little *p*-compound, m.p. 132° , is formed. The sulphonation of toluene leads mainly to the formation of *o*- and *p*-toluene sulphonic acids.

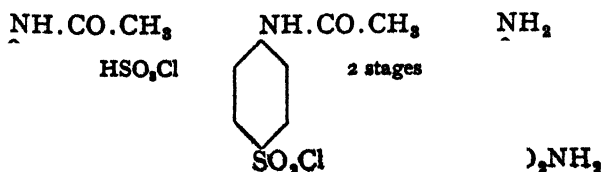
The nitration of benzene sulphonic acid or the sulphonation of nitrobenzene yields in each case a mixture of *o*-, *m*- and *p*-nitrobenzene sulphonic acids, containing a preponderance of the *m*-compound. On reduction these yield the three *aminosulphonic acids*, which are colourless crystalline compounds having acidic, but no basic, properties. The sulphonic acids derived from primary amines may be diazotised and are of value in the preparation of azo-dyes (p. 490).

Sulphanilic acid, *p*-aminobenzene sulphonic acid, is obtained by heating aniline to 180° with fuming sulphuric acid containing 8 to 10 per cent. of anhydride. The properties of sulphanilic acid are strikingly different from those of an aromatic amine or sulphonic acid. It is only slightly soluble in organic solvents and water, is non-volatile, and decomposes without melting above 280° . These properties are best represented by an *inner salt* or *zwitter-ion* formula (*cf.* p. 240), thus resembling an inorganic salt like sodium chloride in being ionised



but differing in not dissociating. The basic properties of the amino group are completely masked, sulphanilic acid, for example, failing to dissolve in hydrochloric acid. As shown above it forms a sodium salt with sodium hydroxide, and the fact that the sodium salt but not the free acid can be acetylated is in harmony with the above representation.

Sulphanilamide, $\text{H}_2\text{N}\cdot\text{C}_6\text{H}_4\cdot\text{SO}_2\text{NH}_2$, the amide of sulphanilic acid, is a valuable remedy for the treatment of streptococcal infections (see index). It is prepared by the sulphonation of acetanilide with chlorosulphonic acid, followed by treatment with ammonia.



Metanilic acid, or *m-aminobenzene sulphonic acid*, is obtained from *m*-nitrobenzene sulphonic acid by reduction with iron and hydrochloric acid.

Sulphinic acids, $R \cdot SO_2H$, may be prepared by reducing arylsulphonic chlorides with zinc dust and water. They are crystalline compounds



which dissolve sparingly in cold water.

VIII

Aromatic Arsenic Compounds¹

Mainly in consequence of the researches of P. Ehrlich, organic compounds of arsenic have been extensively employed in medicine. Only a few of the more important arsenic compounds and their therapeutically important derivatives will be treated here.

It is not surprising that nitrogen and arsenic, belonging as they do to the same group in the periodic classification, should give rise to organic substances of similar type, and a brief inspection of formulæ is sufficient to show the relationship between the nitroso-, azo-, and nitro-compounds on the one hand and the arsine oxides, arseno-compounds, and arsonic acids on the other.

$C_6H_5N : O$	$C_6H_5As : O$
Nitrosobenzene	Phenylarsenoxide
$C_6H_5N : NC_6H_5$	$C_6H_5As : AsC_6H_5$
Azobenzene	Arsenobenzene
$C_6H_5NO_2$	$C_6H_5AsO_2$
Nitrobenzene	Phenylarsonic acid (anhydride)

Arylarsonic Acids

$$\begin{array}{c} \text{OH} \\ \diagup \\ \text{Phenylarsonic acid, } C_6H_5As=O \\ \diagdown \\ \text{OH} \end{array}$$

, is representative of this technically

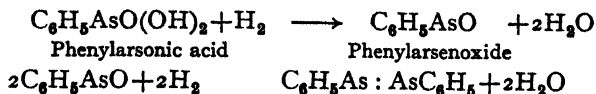
important type of acid and when warmed loses water to give the anhydride analogous to nitrobenzene (see above). It will be noted, however, that while a hydrate of nitrobenzene is unknown it is the hydrate of the arsenic compound which is stable. The arsonic acids are prepared by the action of sodium arsenite on diazonium salts (*Bart's reaction*), *e.g.* :—



Phenylarsonic acid itself may conveniently be prepared by elimination of the amino-group from *p*-aminophenylarsonic acid (see p. 497).

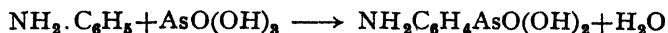
¹ L. F. Hewitt, H. King and W. O. Murch, *J.*, 1925, 1355. *The Basis of Chemotherapy* by T. S. Work and E. Work (Oliver and Boyd, 1948). *Text-book of Inorganic Chemistry*, (Editor, J. Newton Friend), Vol. xi., Part II.

The arylarsonic acids are crystalline substances which can be reduced to derivatives of trivalent arsenic. Phenylarsonic acid, for example, with a mild reducing agent such as sulphurous acid and a little hydrogen iodide as catalyst yields phenylarsenoxide, which on further reduction with phosphorous acid gives arsenobenzene.



p-Aminophenylarsonic acid, *Arsanilic acid*, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{AsO}(\text{OH})_2$ is one of the most important of the arsonic acids. It was first prepared in 1863 by Béchamps by heating aniline arsenate and was employed under the name of **atoxyl**. Béchamps considered it to be an anilide of arsenic acid, but Ehrlich and Bertheim assigned to it the correct structure.

In general, when primary aromatic amines are fused with arsenic acid, the arsenic group takes up the para-position with respect to nitrogen, with the formation of *p*-aminoaryl arsonic acids. If the *p*-position is already occupied, then either no substitution occurs or the corresponding *o*-amino-derivative is obtained :



Many other aromatic compounds, such as phenols and certain indoles behave in the same manner. The process is an exact parallel to the production of sulphanilic acid by the action of heat on aniline sulphate (p. 495) and may therefore be described as **arsenation** (*cf.* sulphonation) and the reaction products as **arsanilic acids**.

p-Aminophenylarsonic acid is the most important of these acids, and, as already described, is obtained by the arsenation of aniline. It is a crystalline colourless compound which dissolves in hot water to give an acid solution. As an acid it is readily soluble in alkalis, but it also possesses basic properties, as shown by its solubility in an excess of dilute mineral acid. The sodium salt was formerly employed in medicine under the name of **atoxyl** in cases of syphilis and sleeping sickness. In 1905 Thomas and Breinl in the University of Liverpool found that **atoxyl** cured trypanosomiasis in mice. This successful therapeutic application of **atoxyl** led Ehrlich to carry out his important researches on the clinical application of arsenical drugs culminating in the synthesis and use of salvarsan (see below). For his achievements in the field of chemotherapy Ehrlich was awarded the Nobel Prize in 1909.

Reduction Products of Arsanilic Acids.

pp'-Diamino-arsenobenzene¹

On energetic reduction the arylarsonic acids are converted into arseno-compounds, that produced from *p*-aminophenyl arsonic acid (arsanilic

¹ P. Ehrlich and Bertheim, *Ber.*, 1911, 44, 1260.

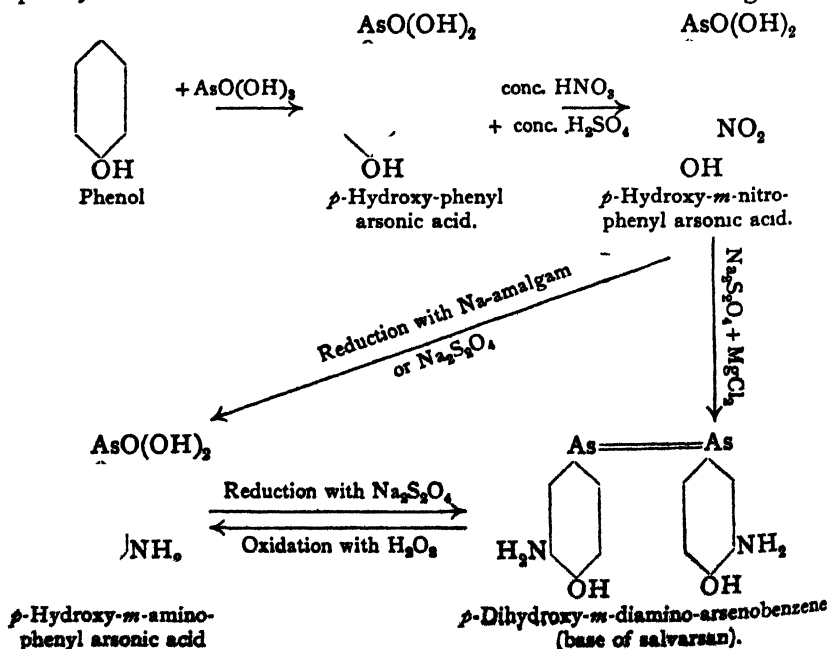
acid) being *pp'*-diamino-arsenobenzene or *p*-arsenoaniline, possessing the structure



This compound can be prepared in a variety of ways, such as by the reduction of *p*-aminophenyl arsonic acid with sodium hydrosulphite, or with stannous chloride and hydriodic acid. It melts at 260° , is insoluble in water and aqueous alkalis, but as a base is readily soluble in dilute hydrochloric acid. Oxidising agents attack it rapidly, as the arseno-compounds in general are characterised by strong reducing properties. Diamino-arsenobenzene also gives the reactions of primary amines. It is readily diazotised, converted into azo-dyes, and condensed with aldehydes.

The reduction of *p*-aminophenyl arsonic acid to diamino-arsenobenzene is found to bring about a great increase in toxic power and also in trypanocidal action, in explanation of which it has been suggested that the chemoceptors of the parasites are able to attach themselves to the trivalent but not to the pentavalent arsenic residue. The belief that only those radicals containing trivalent arsenic exert a direct trypanocidal action led to the examination of other arsenic compounds and to the isolation of salvarsan.

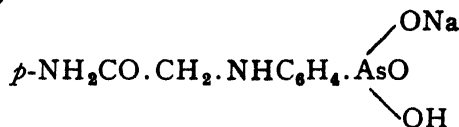
Salvarsan or "606."—This compound, the hydrochloride of which, under the name of salvarsan or arsphenamine excited such general interest in the medical world, was prepared from *p*-hydroxy-phenyl-arsonic acid. The latter was obtained directly from phenol and arsenic acid, in the same manner as phenolsulphonic acid is obtained from phenol and sulphuric acid. It was then nitrated, and the resulting *p*-hydroxy-*m*-nitrophenyl arsonic acid reduced as indicated in the following scheme:



Salvarsan, the dihydrochloride of *p*-dihydroxy-*m*-diamino-arsenobenzene, whose formula is given above, is a yellow, crystalline powder, readily soluble in water, methyl alcohol and glycerol. A point requiring careful attention in its practical use is that, like other arseno-compounds, it is readily oxidised. When exposed to the air it rapidly acquires a proportion of the far more poisonous *amino-hydroxy-phenylarsine oxide*. As an injection of such a preparation would be dangerous for the patient, salvarsan is preserved in evacuated tubes, or in ampoules which have first been exhausted and then filled with an indifferent gas.

Salvarsan has proved a valuable specific for certain dangerous protozoal diseases, particularly syphilis.

Tryparsamide and Orsanine.—Tryparsamide, the most widely used arsenical in the treatment of trypanosomiasis, was discovered in 1919 by Jacobs and Heidelberger at the Rockefeller Institute. It is a derivative of atoxyl (p. 497)



(sodium *N*-phenylglycinamide *p*-arsonate) and is prepared from atoxyl and excess chloracetamide. Tryparsamide, which has only one-twentieth of the toxicity of salvarsan, is used in the treatment of sleeping sickness and syphilis. The pentavalent arsenicals like tryparsamide are not trypanocidal *sui generis*, but become effective by reduction in the host to the trivalent form.

Another arsenical as effective as tryparsamide is **orsanine**, a French pro-

duct with the formula

$$\begin{array}{l} (4) \text{CH}_3\text{CONH} \\ (2) \text{HO} \end{array} \begin{array}{c} \nearrow \\ \searrow \end{array} \text{C}_6\text{H}_4\text{AsO} \begin{array}{l} \nearrow \text{ONa} \\ \searrow \text{OH} \end{array} \quad \text{Unlike salvarsan}$$

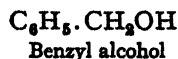
or neosalvarsan, orsanine can pass from the blood into the cerebro-spinal fluid and attack the trypanosomes there. Other drugs of this type which show great promise have been introduced by Friedheim: e.g. *melarsen* in which the amino group of atoxyl is replaced by a melaminyl residue.

IX

Phenols

The phenols are substances in which one or more hydrogen atoms of the benzene nucleus are replaced by hydroxyl groups. They are to be contrasted with those aromatic substances which contain the hydroxyl group in a side-chain and which are known as aromatic alcohols (p. 518).

m-Cresol, for example, is a typical phenol while the isomeric benzyl alcohol is devoid of phenolic characteristics and behaves as a derivative of ethanol.



Such isomers are readily distinguished by oxidation, *m*-cresol giving *m*-hydroxybenzoic acid, and benzyl alcohol giving benzoic acid.

Phenols are described as mono-, di-, and tri-hydric phenols according as they contain one, two, or three nuclear hydroxyl groups. The monohydric phenols in particular are formed during the dry distillation of wood and coal, and hence are present in coal-tar, from the carbolic oil of which they are obtained industrially (p. 427). It was from this source that phenol was first isolated in 1834 by Runge. Phenols may be prepared by a number of methods including the fusion of sulphonic acids with sodium or potassium hydroxide (p. 494) or by heating diazonium salts with water (p. 479). Other methods are described under individual phenols.

Properties and Reactions.—The structural resemblance of the phenols to the tertiary alcohols is reflected in the similarity of their chemical properties. They form, for instances, esters such as *phenyl acetate* and ethers such as *anisole*, $\text{C}_6\text{H}_5\text{OCH}_3$. They differ markedly from the alcohols, however, in possessing slight but distinct acidity due to the negativity of the phenyl nucleus, *i.e.* to the tendency of the phenyl nucleus to attract electrons thereby facilitating the removal of a proton from the phenolic group. This property is exemplified by the ease with which phenols dissolve in aqueous alkali to form salts such as *sodium phenoxide*, $\text{C}_6\text{H}_5\text{ONa}$, and by the formation of methyl ethers by means of diazomethane, a reagent which does not methylate alcoholic groups.

The hydroxyl group may be replaced by other groups and atoms. By the action of phosphorus pentachloride the hydroxyl group of a phenol can be replaced by chlorine, though much less readily than in the case of the alcohols. Replacement by the amino-group is effected by heating with the zinc chloride-ammonia compound. Finally the hydroxyl group may be replaced by hydrogen by fusing phenols with zinc dust, a reagent first used by Baeyer to remove oxygen from aromatic compounds. This method is of great importance in determining the structure of organic compounds, especially substances of complex structure, since it yields the parent hydrocarbon from which the phenol is derived. Graebe and Liebermann thus showed that the dyestuff alizarin is an anthracene derivative since it yields this hydrocarbon when distilled with zinc dust (p. 597). A useful modification of the method involves fusion with zinc dust in zinc chloride.¹

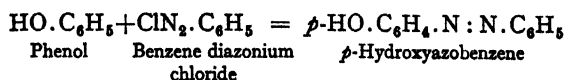
The ease of substitution of the phenols has already been emphasised (p. 436) and is illustrated by the ready formation of 2 : 4 : 6-tribromophenol

¹ E. Clar and Fr. John, *Ber.*, 1931, 64, 981.

by bromination without a catalyst. Under comparable conditions, but with a catalyst benzene gives bromo- and *p*-dibromo-benzene.

The benzene ring is not readily oxidised ; but phenols, and particularly the polyhydric phenols, are very susceptible to oxidising agents. Slightly impure phenol when exposed to the air forms coloured oxidation products, and catechol in alkaline solution is oxidised to carbon dioxide by a current of air. *o*- and *p*-Dihydric phenols are oxidised to *quinones* (p. 511).

Phenols "couple" or condense very readily in alkaline solution with diazonium compounds (p. 490) to give azo-products, many of which are of importance in the dyestuffs industry. Thus phenol and benzene diazonium chloride in alkaline solution yield *p*-hydroxyazobenzene.



Phenols are frequently detected by colour tests. They give characteristic colours with ferric chloride, phenol itself giving a violet colour. Many of them give the *phthalein test* when heated with phthalic anhydride and zinc chloride or sulphuric acid. In this test phenol and *o*-cresol give a red colour ; *m*-cresol and catechol a blue colour ; and resorcinol a fluorescent green solution.

Phenols also react with nitrous acid to give products which are discussed later (p. 514).

Certain other reactions which are peculiar to polyhydric phenols are described later.

A large industry arose out of the discovery by Baekeland that synthetic resins or *bakelites* can be prepared by condensing formaldehyde with phenols such as phenol and cresol. Such resins are readily coloured and moulded, and are employed in ever-increasing quantities for electrical insulators and the manufacture of a variety of articles. A further description of these products is given later (see synthetic resins).

1. Monohydric Phenols and their Derivatives

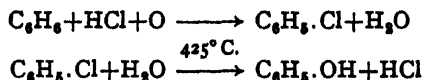
Phenol, *carbolic acid*, $\text{C}_6\text{H}_5\text{OH}$, is the chief constituent of that fraction of coal tar boiling at 170° to 230° , and generally known as middle or carbolic oil. It is prepared from this source, after removal of naphthalene, by extracting with dilute caustic soda. The aqueous layer is run off and phenol precipitated with sulphuric acid or carbon dioxide. Finally it is purified by distillation.

Although chlorobenzene is not readily hydrolysed under ordinary conditions it is converted into phenol when heated with sodium hydroxide at 350°C . and 200-300 atmospheres pressure in presence of a copper catalyst.



Great quantities of phenol are now manufactured by this process.

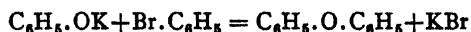
Phenol is also prepared in Germany and the U.S.A. by the *Raschig process* in which benzene is chlorinated with hydrochloric acid and air over a catalyst at 230° , the chlorobenzene so formed being hydrolysed with steam.



In the pure form phenol is a white crystalline substance, m.p. 43° . It is liquefied on addition of a very small proportion of water, and dissolves completely in 15 parts at 20° . It possesses a peculiar pungent smell, is poisonous, and is employed in aqueous solution (*e.g.* 3 per cent.) as a disinfectant. Indeed modern asepsis began with the use of phenol (carbolic) in 1865 by Lister, who showed that with the help of this chemical post-operational sepsis could to a large extent be eliminated. Since that time many phenolic derivatives have been tested for antibacterial activity and some such as trichlorophenol, hexylresorcinol (*4-n-hexyl-resorcinol*) and ethyl *p*-hydroxybenzoate have been used medicinally.

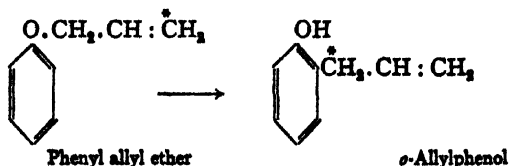
Phenol dissolves readily in alkali hydroxides with the formation of sodium and potassium phenates, these being obtained in the solid state when the solutions are evaporated. Phenol is used in large quantities for the production of bakelite resins and the commercial preparation of cyclohexanol and cyclohexanone.

Phenol reacts with dimethyl sulphate and alkali to give the methyl ether, **anisole**, $\text{C}_6\text{H}_5\cdot\text{OCH}_3$, a colourless liquid, b.p. 155° with a characteristic smell. The ethyl ether, **phenetole**, b.p. 172° , is similarly prepared by means of diethyl sulphate. The phenyl ether, **diphenyl ether**, $\text{C}_6\text{H}_5\cdot\text{O}\cdot\text{C}_6\text{H}_5$, is best prepared by heating potassium phenoxide with bromobenzene in the presence of finely divided copper.



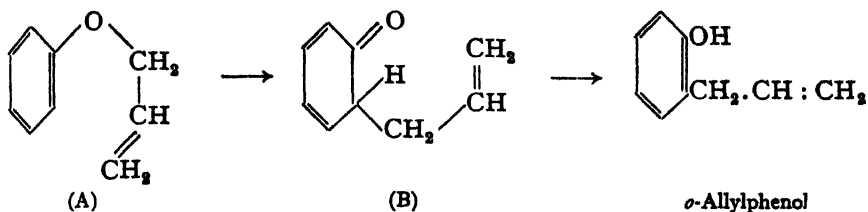
The ethers are stable substances which are hydrolysed only with difficulty by the use of reagents such as boiling hydriodic acid or hydrobromic acid. They are less reactive than phenol, anisole, for example, with bromine giving 2 : 4-dibromoanisole (*cf.* the bromination of phenol).

Phenolic ethers containing the allyl group when heated undergo an interesting intramolecular change known as the *Claisen Rearrangement*.



Phenyl allyl ether, for instance, when heated to 200° gives *o*-allylphenol. The reaction occurs without the aid of a catalyst and the yields are nearly quantitative. The migration generally takes place to the *ortho*-position;

sometimes to the *para*-, but never to the *meta*-position. It is characteristic of the *ortho*-migration that inversion occurs; *i.e.* it is the end carbon atom of the side-chain (marked with an asterisk) which attaches itself to the benzene ring. The change can be pictured by the ether adopting the configuration A, which by a shift of electrons changes into B. This is merely the unstable form of *o*-allylphenol. This mechanism¹ is



supported by experimental evidence. The ethyl compound (C) undergoes the rearrangement to give the product (D) and this clearly shows it is the "end carbon atom" which unites with the nucleus. Moreover,



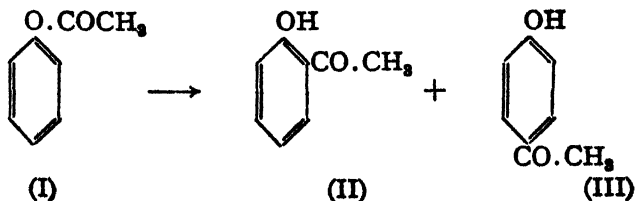
(C)

(D)

kinetic measurements show that the rate of change is proportional to the concentration of the ether, which means that the rate-determining step involves only a single molecule of the ether.

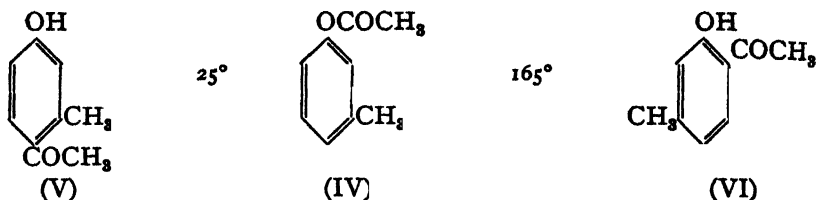
The *para*-rearrangement occurs without inversion and its mechanism must differ from that of the *ortho*-rearrangement.²

Fries Rearrangement.³—Fries in 1908 found that the phenolic esters of carboxylic acids in the presence of aluminium chloride undergo a change, now known as the *Fries Rearrangement*, in which the acyl group migrates to a position *ortho* or *para* to the hydroxy group, but never to the *meta*. In the simplest example, phenyl acetate (I) is converted into a mixture of *ortho*- and *para*-hydroxyacetophenones (II and III). The ratio of the *ortho*- to the *para*-product depends on the temperature,



¹ C. H. Hurd and M. A. Pollack, *J. org. Chem.*, 1938, 3, 550. E. R. Alexander and R. W. Kluiber, *J.A.C.S.*, 1951, 73, 4304. For a review of the reaction, see S. Tarbell, *Organic Reactions* (Editor, Roger Adams), vol II, p. 1. ² For recent work see N. Campbell, *Ann. Rev.*, 1953, 50, 196. ³ A. H. Blatt, *Chem. Reviews*, 1940, 27, 413. *Organic Reactions* (Editor, Roger Adams), vol. I, Chap. 2.

m-cresyl acetate (IV) for example, yielding at 25° only 2-methyl-4-hydroxy-acetophenone (V) and at 165° only 2-hydroxy-4-methylacetophenone (VI). This is most simply explained by assuming that the



reaction is reversible ; and that V is formed more rapidly than VI, though VI is more stable. This is confirmed by the fact that the *para* isomer (V) is converted into the *ortho*-isomer (VI) by heating at 165° with aluminium chloride. In general the *ortho*-compounds are more stable than the *para*-products, possibly owing to chelation of the former.

Esters of phenols are produced by the action of acid chlorides or anhydrides on phenols or their alkali salts. Like the esters of aliphatic alcohols they are decomposed into their components when heated with alkalis. The sulphuric and glucuronic esters of phenols and of many heterocyclic hydroxy-compounds which are eliminated in the urine play an important part in the animal organism, since by union with acids the phenols lose their poisonous character

2. Homologues of Phenol

The cresols, $\text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{OH}$, may be regarded either as methyl derivatives of phenol or as hydroxy derivatives of toluene. They are obtained from coal-tar, and since they are cheaper than phenol they are much used as disinfectants of the *Lysol* type. For these preparations the crude cresols are rendered soluble in water by the addition of resin soap or oil soap.

TABLE

Phenol	m.p.	b p.
<i>o</i> -Cresol	31°	191°
<i>m</i> -Cresol	12°	203°
<i>p</i> -Cresol	36°	202°
<i>o</i> -3-Xylenol *	73°	213°
<i>o</i> -4-Xylenol *	65°	222°
<i>m</i> -5-Xylenol *	64°	220°
Thymol	51°	234°
Carvacrol	1°	238°

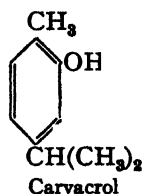
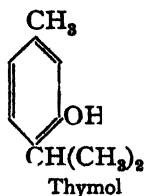
* In these substances the letter refers to the positions of the methyl groups and the number to that of the hydroxyl group *E.g.* *o*-3-Xylenol is 3-hydroxy-1 : 3-dimethylbenzene.

The structure of the cresols follows from the oxidation of their methyl ethers. Thus *p*-Cresol when methylated yields *p*-cresyl methyl ether, which is oxidised by potassium permanganate to anisic acid. Chemically

the cresols resemble phenol closely. They give bright colours with ferric chloride; form nitroso-compounds with nitrous acid; and are readily nitrated and halogenated. They sometimes differ, however, from phenol. *o*-Cresol with bromine gives not the expected brominated cresol but tribromotoluquinone, bromination being accompanied by oxidation. *m*-Cresol with bromine gives the expected tribromo-*m*-cresol, but with chlorine is oxidised to trichlorotoluquinone.

The six xylenols are dimethylphenols and are obtained from coal-tar. *m*-5-Xylenol gives the 4-chloro-compound which is used in antiseptics of the *Dettol* type.

Two phenols which are derivatives of *p*-cymene are thymol and carvacrol. **Thymol** is one of the oldest known phenols and occurs with *p*-cymene and thymene in oil of thyme and other essential oils. It has the pleasant smell of thyme and is used as an antiseptic. **Carvacrol**, isomeric with thymol, is the main constituent of origanum oil. Since both substances can be prepared from *p*-cymene they differ only in the position of the hydroxyl group. Thymol must have its hydroxyl group *ortho* to the *isopropyl* group since on reduction it gives a mixture of the stereoisomeric menthols (p. 398).



Carvacrol must therefore possess a hydroxyl group *ortho* to the methyl group and this is confirmed by the aromatisation of carvone (p. 451) to carvacrol by means of acids.

Phenylsulphuric acid, *phenolsulphuric acid*, $\text{C}_6\text{H}_5\cdot\text{O}\cdot\text{SO}_3\text{H}$, is unknown in the free state. The potassium salt occurs in urine, and may be prepared from potassium phenate by heating it with potassium pyrosulphate. When heated in a sealed tube the salt isomerises into potassium *p*-phenolsulphonate, $\text{C}_6\text{H}_5\cdot\text{O}\cdot\text{SO}_3\text{K} \rightarrow \text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{SO}_3\text{K}$.

NITRO- AND AMINO-DERIVATIVES OF PHENOL

The hydroxyl group like the amino group greatly facilitates further substitution in the benzene molecule, and it is therefore not surprising that phenol is very easily nitrated, and yields according to conditions, mono-, di-, or tri-nitrophenols, in which the nitro-group substitutes almost entirely in the *o*- and *p*-positions to the hydroxyl. Even dilute nitric acid can nitrate phenol.

o- and *p*-Nitrophenols are obtained by the nitration of phenol and are separated by distillation in steam in which only the *ortho*-compound is volatile, *p*-nitrophenol remaining behind. *m*-Nitrophenol is obtained by

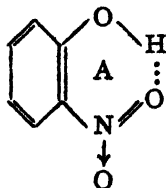
the diazotisation of *m*-nitraniline. With a stronger nitrating agent phenol yields 2 : 4-dinitrophenol and with concentrated sulphuric acid and concentrated nitric acid gives picric acid, 2 : 4 : 6-trinitrophenol. The ease of preparation of picric acid is in sharp contrast to the difficulty of preparing 1 : 3 : 5-trinitrobenzene by the nitration of benzene.

	m.p.	b.p.	k_a
<i>o</i> -Nitrophenol . . .	45°	214°	6.8×10^{-8}
<i>m</i> -Nitrophenol . . .	96°	..	3.9×10^{-8}
<i>p</i> -Nitrophenol . . .	114°	295°	7.0×10^{-8}
2 : 4-Dinitrophenol . .	113°	..	1.0×10^{-4}
Picric acid . . .	122°	..	1.6×10^{-1}

The presence of the nitro-group increases the acidity of the phenol (k_a 1.09×10^{-10}) so that the nitro-phenols are sufficiently strong acids to decompose carbonates.

The nitro-phenols have many interesting properties. The *ortho*-compound is yellow, whereas *p*-nitrophenol and 2 : 4-dinitrophenol are colourless. With alkali all three mononitrophenols give coloured salts, sodium *o*-nitrophenolate being obtained in dark red prisms, and the *para*-isomer as golden yellow crystals. The cause of colour in these salts has been the subject of much speculation by Hantzsch and others but no completely satisfactory explanation has yet been advanced.

o-Nitrophenol differs markedly in many of its properties from the *m*- and *p*-isomers. As we have seen it is very volatile in steam whereas the *p*-isomer is non-volatile. Its boiling-point is also anomalous. Generally the introduction of a nitro-group into a molecule raises the boiling-point considerably, but the boiling-point of *o*-nitrophenol (214°) is not very much higher than that of phenol (181°). Again *o*-, *m*-, and *p*-isomers usually boil within a few degrees of one another (*e.g.* xylenes, toluidines, cresols, etc.), but *o*-nitrophenol boils about 80 degrees below *p*-nitrophenol (295°). Another striking property of *o*-nitrophenol is the solubility in organic solvents such as benzene and the small solubility in water. It is, for example, one-fifth as soluble in water as the *p*-compound and 127 times as soluble in benzene. These characteristics furnish strong reasons for the belief that the phenolic hydroxyl group is partly



suppressed (Sidgwick) by the interaction of the nitro and hydroxyl groups with the formation of a *chelate ring* (A) (p. 90). In other words we have an example of *intramolecular hydrogen bonding* in which the

hydrogen atom of the phenolic group links the oxygen of that group with an oxygen atom of the nitro-group with the formation of an association link (marked by a dotted line in the formula). The suppression of the phenolic group results in a smaller polarity of the nitrophenol molecule, thereby lowering its power of association (*e.g.* lower boiling-point and greater volatility) and solubility in hydroxylic solvents and increasing its solubility in hydrocarbon solvents.

It is obvious that the formation of the chelate ring is dependent on the close proximity of the nitro and hydroxyl groups in *o*-nitrophenol, and that no such effect will be observed in the *m*- and *p*-isomers. It is an example of what is known as the *ortho-effect*, and other examples will be found on pp. 90, 449.

Chelate rings are always five- or six-membered rings which are coplanar with the ring to which they are fused. They generally contain a couple of double bonds. The strength of the association linkage is about one-twentieth of the normal co-valent bond.

Picric acid, 2 : 4 : 6-*trinitrophenol*, crystallises in pale yellow plates, m.p. 122°, and is prepared on the large scale by nitrating phenol with a mixture of sulphuric acid and nitric acid. It was formerly used as a dye, but is now used mainly as a powerful explosive. When suddenly heated or detonated by mercury fulminate it decomposes according to the equation, $C_6H_2(NO_2)_3.OH = 6CO + H + 3N + H_2O$. Picric acid is known commercially by various names *e.g.* lyddite in Great Britain, mellinite in France.

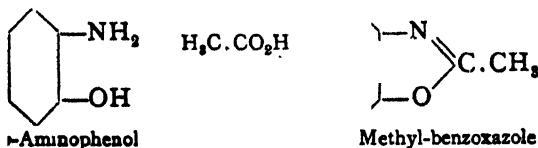
As would be expected from the presence of the three nitro groups in the *ortho*- and *para*-positions to the hydroxyl group picric acid is characterised by its strongly acidic nature. This is shown not only by its k_a (see table) but also by the ease with which it reacts with phosphorus chloride to form picryl chloride, $C_6H_2(NO_2)_3.Cl$. This replacement of hydroxyl by chlorine closely resembles the formation of acid chlorides from carboxylic acids and phosphorus pentachloride. Like the acid chlorides picryl chloride is very reactive, and with ammonia gives picramide, $C_6H_2(NO_2)_3.NH_2$, m.p. 188°.

Picric acid unites with many aromatic hydrocarbons, such as naphthalene and anthracene, to form beautifully crystalline coloured molecular compounds, which are of service in the recognition and isolation of these hydrocarbons. These *picrates* are characterised by their strong yellow, orange, or red colour in contrast to the lack of colour or at least of pronounced colour in the components. These generally combine in a simple 1 : 1 molecular ratio.

On reduction the nitrophenols give aminophenols, in the same way as nitro-hydrocarbons yield amino-compounds. Aminophenols, as would be expected, are both acids and bases. In the free state they readily undergo decomposition, but the hydrochlorides are more stable.

o-Aminophenol, $NH_2.C_6H_4.OH$, melts at 170°, and its methyl ether, *o*-anisidine, $NH_2.C_6H_4.OCH_3$, is a liquid of b.p. 218°. Like the

o-phenylene diamines, the *o*-aminophenols tend to form cyclic compounds, e.g. with carboxylic acids they yield *benzoxazoles*,



***p*-Aminophenol**, m.p. 184° , is formed when *p*-nitrophenol is reduced with iron and hydrochloric acid, and is best prepared by the electrolytic reduction of nitrobenzene in strong sulphuric acid solution (see p. 455). Its methyl derivative, $\text{CH}_3 \cdot \text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{OH}$, known as **metol**, is also used for the same purpose. *p*-**Phenetidine**, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OC}_2\text{H}_5$, the ethyl ether of *p*-aminophenol, is employed in the preparation of **phenacetine** (*p*-ethoxy-acetanilide), $\text{CH}_3\text{CO} \cdot \text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{OC}_2\text{H}_5$, m.p. 135° , which is used as an antipyretic and in cases of neuralgia.

2 : 4-Diaminophenol, obtained from 2 : 4-dinitrophenol, is also of interest, as its sodium salt is employed as a photographic developer under the name of **amidol**.

3. Dihydric Phenols and their Derivatives

In the main the di- and polyhydric phenols closely resemble the monohydric compounds in their properties, but many of them are strong reducing agents in alkaline solution. They are generally prepared from the di- or polysulphonic acids of aromatic hydrocarbons, or from phenol-sulphonic acids, by fusion with potassium hydroxide. According to the relative positions of the two hydroxyl groups the dihydric phenols show characteristic differences in chemical behaviour.

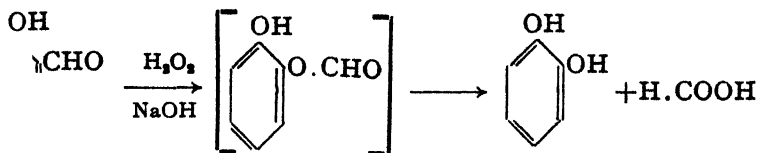
The *ortho*-compounds frequently give green colorations with ferric chloride, and readily yield heterocyclic derivatives in which the two hydrogen atoms of the hydroxyl groups are replaced by a divalent radical.

The *meta*-compounds usually give a deep violet coloration with ferric chloride, and undergo the fluorescein reaction, *i.e.*, when heated with phthalic anhydride they yield *phthaleins*, which show a green fluorescence in alkaline solution.

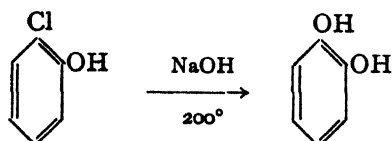
The *para*-compounds on oxidation very easily pass into quinones, which are readily recognised.

Catechol, *pyrocatechin*, *o*-**dihydroxy-benzene**, $\text{C}_6\text{H}_4(\text{OH})_2$, m.p. 105° , has been obtained from catechin, moringatannic acid, kinotannic acid and other sources containing tannic acids. It is formed from the mono-methyl ether, *guaiacol*, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{OCH}_3$, which occurs in the crude creosote of beech tar, by demethylation (boiling with hydrobromic acid or by heating with aluminium chloride). It can also be obtained in moderate yield by the *Dakin reaction*, a method applicable to *o*- and *p*-hydroxy derivatives of aromatic aldehydes. Salicylaldehyde is oxidised

with an alkaline solution of hydrogen peroxide, the aldehydic group being removed as formic acid and replaced by the hydroxyl group.



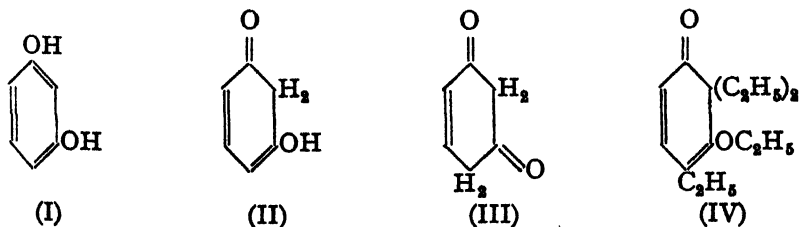
Catechol is prepared technically by heating *o*-chlorophenol under pressure with sodium hydroxide (*cf.* preparation of phenol).



An aqueous solution of catechol gives a green colour with ferric chloride, which changes to deep red on the addition of alkalis, alkali carbonates or ammonia. A physiologically important derivative of catechol is adrenaline.

Resorcinol, *m*-*dihydroxy-benzene*, $\text{C}_6\text{H}_4(\text{OH})_2$, m.p. 110° , is prepared technically by fusing benzene disulphonic acid with alkali at 235° to 270° . It readily dissolves in water. It yields fluorescein on being heated with phthalic anhydride, and is used in the preparation of dyes. With cold nitric acid it yields a trinitro-derivative known as *styphnic acid*, m.p. 175° .

Many phenols are completely enolic. In other words they show no sign of undergoing tautomeric change to the keto form. Resorcinol, however, reacts not only in the enolic form (I) but also in the ketonic forms II and III. As an enol it gives a deep violet colour with ferric



chloride; forms a dibenzoate; and with ethyl iodide affords resorcinol diethyl ether, $\text{C}_6\text{H}_4(\text{OC}_2\text{H}_5)_2$. In the last mentioned reaction, however, a tetraethyl derivative of resorcinol (IV) is also obtained, corresponding to the keto-enolic structure (II). Resorcinol combines with sodium bisulphite to give a product which is in all probability the bisulphite compound of 3 : 5-*diketo-hexamethylene-1-sulphonic acid*. The formation of this substance may be explained¹ on the assumption that it is derived from the tautomeric form of resorcinol, III.

¹ W. Fuchs and Elsner, *Ber.*, 1920, 53, 886; 1924, 57, 1225.

n-Hexylresorcinol, *Caprokol*, ($\text{OH} : \text{OH} : \text{C}_6\text{H}_{13} = 1 : 3 : 4$), is a valuable internal antiseptic of high germicidal value (*cf.* p. 502).

Hydroquinone, *quinol*, *p*-*dihydroxy-benzene*, m.p. 170° , is prepared by reducing quinone with sulphurous acid, and by virtue of its reducing properties is used as a photographic developer. With oxidising agents it is easily converted into quinone. Sodium bisulphite unites with hydroquinone to give 1:4-*dihydroxy-hexamethylene-1:2:4-trisulphonic acid*. This reaction, as well as certain changes which take place in the hydroquinone developer, are explained on the assumption that hydroquinone may also react in tautomeric form as an unsaturated cyclic ketone.

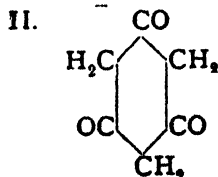
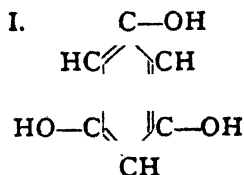
Of the six dihydroxy-toluenes, $\text{CH}_3 \cdot \text{C}_6\text{H}_3(\text{OH})_2$, the most important is orcinol, 3 : 5-*dihydroxy-toluene*, which may be regarded as a homologue of resorcinol. It occurs in the free and combined state in many lichens of the *Roccella* and *Leconora* families, and may be obtained from *orsellinic acid* by boiling with lime, or synthetically from acetone-dicarboxylic ester. Orcinol crystallises with 1 mol. H_2O in colourless prisms, m.p. 107° and b.p. 290° .

4. Trihydric Phenols and their Derivatives

All of the three possible isomerides expected on theoretical grounds are known, viz., pyrogallol, phloroglucinol and hydroxy-hydroquinone.

Pyrogallol, *pyrogalllic acid*, 1:2:3-*trihydroxy-benzene*, is prepared by heating gallic acid, $\text{C}_6\text{H}_3(\text{OH})_3 \cdot \text{COOH} = \text{C}_6\text{H}_3(\text{OH})_3 + \text{CO}_2$. It forms white plates, m.p. 132° , which dissolve readily in water. In alkaline solution it turns brown owing to absorption of oxygen, and hence is sometimes used for estimating oxygen in gas analysis. Owing to its reducing properties it is also employed as a developer in photography.

Phloroglucinol, 1:3:5-*trihydroxy-benzene*, $\text{C}_6\text{H}_3(\text{OH})_3$, melts at 218° , and is obtained as a disruption product of certain complex substances, *e.g.* from many resins by fusion with potash. It is best prepared from symmetrical triamino-benzene or symmetrical triaminobenzoic acid by heating with acids. Phloroglucinol, like resorcinol, exhibits keto-enolic tautomerism, reacting not only in the phenolic form, I, but also as a hexamethylene triketone, II.



Thus as a phenol it yields a trimethyl ether, $\text{C}_6\text{H}_3(\text{OCH}_3)_3$, and a triacetyl derivative, $\text{C}_6\text{H}_3(\text{O} \cdot \text{CO} \cdot \text{CH}_3)_3$, and as ketone it forms a trioxime, $\text{C}_6\text{H}_3(\text{NOH})_3$.

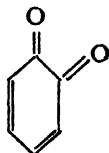
Corresponding to the thioalcohols and the alkyl sulphides are the thiophenols, *e.g.* $\text{C}_6\text{H}_5 \cdot \text{SH}$, and the phenyl sulphides. They are of little importance and cannot be described here.

X

Quinone and Quinonoid Derivatives

Quinones and Quinonoid Compounds

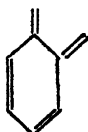
The quinones are substances in which two hydrogen atoms of the benzene nucleus are replaced by two oxygen atoms, the products being distinguished as *o*- and *p*-quinones according to the relative positions of the oxygen atoms. The simplest examples are *o*- and *p*-benzoquinone. No *m*-quinone has been isolated. In polynuclear aromatic quinones the carbonyl groups may be situated in different aromatic rings (see, e.g. p. 584).

*o*-Benzoquinone*p*-Benzoquinone

The *o*-quinones of benzene are generally unstable and difficult to isolate. *o*-Benzoquinone is obtained by the oxidation of catechol with silver oxide under anhydrous conditions (R. Willstätter). The *o*-quinones, however, are stabilised by substituents especially in the 3- and 4-positions. Thus 3 : 4 : 5 : 6-tetrachlorocatechol on oxidation yields the stable tetrachloro-*o*-benzoquinone.

Of greater importance are the *p*-isomers which were the first to be discovered and were described shortly as quinones by which name they are still known. It is these compounds and their derivatives which are described in this chapter.

Substances containing the structures A and B are described as *ortho*-quinonoid and *para*-quinonoid. The extra-annular double bonds may be linked to oxygen atoms to give quinones, or to other groups such as the imino-group (NH) or arylimino-group (NR). Examples of the latter types are quinone-imine and quinone-diimine, and the indophenols (pp. 516, 517).



(A)

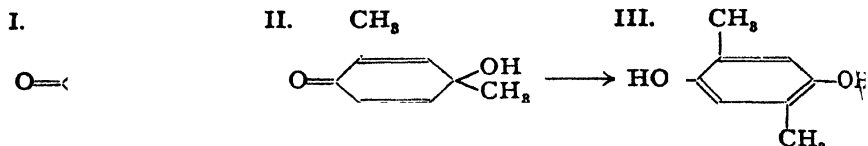


(B)

The quinones have been intensively investigated partly because of the importance of naturally occurring quinones such as vitamins K₁ and K₂, but chiefly because many dyestuffs are quinonoid or at least potentially

so. In consequence the quinonoid structure has played a significant role in the attempted correlation between colour and chemical constitution

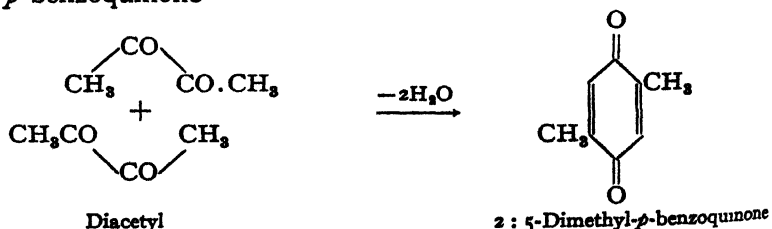
Quinonoid substances have a great tendency to change over to the aromatic type (containing a benzene nucleus with three double bonds) and this tendency leads to remarkable movements of the side-chains in the molecule. It has been shown for instance that the quinol complex I is transformed into the corresponding aromatic structure by the migration of either the hydroxyl or methyl group to another position in the nucleus



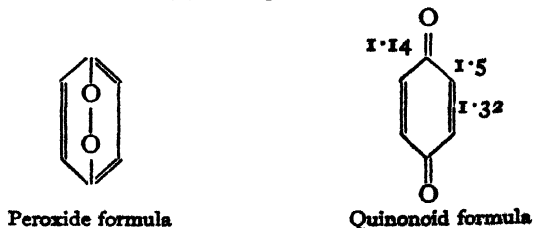
according to the experimental conditions. An example of this type of aromatisation is the isomerisation of 2:4-dimethylquinol (II) into 2:5-dimethylhydroquinone (III).

p-Benzoquinone

p-Benzoquinone (*benzoquinone*) is a typical *p*-quinone and its properties may be taken as representative of this class of compound. Benzoquinone is prepared by the oxidation of many monosubstituted and *p*-disubstituted amino- or hydroxy-benzenes. It is obtained in the laboratory by oxidising aniline with sodium dichromate and sulphuric acid, or by oxidising hydroquinone with this reagent or preferably with sodium chlorate in the presence of vanadium pentoxide as a catalyst. Quinones can also be synthesised from aliphatic diketones. Thus two molecules of diacetyl in the presence of alkali condense to yield 2:5-dimethyl-*p*-benzoquinone



Structure.—Two formulæ have received serious consideration: (1) the peroxide formula, and (2) the quinonoid formula.



Decisive evidence in favour of the latter formula comes from the X-ray analysis of benzoquinone which shows that the molecule possesses the planar quinonoid structure. Moreover the bond lengths (shown in the formula) clearly establish the presence of two $C=C$, four $C-C$, and two $C=O$ bonds as required by the quinonoid structure.¹ The formula expresses adequately the chemical behaviour of benzoquinone.

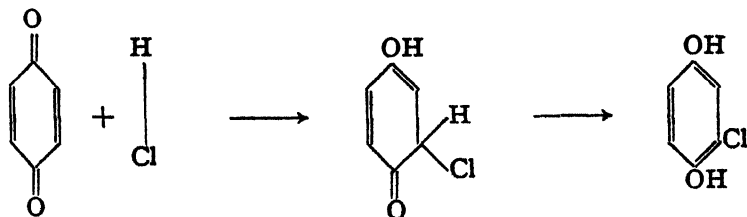
Benzoquinone is a resonance hybrid with a resonance energy of 16Kcal. The main contributing form is the quinonoid structure with minor contributions from polar forms in which the oxygen atoms assume positive and negative charges and the quinonoid ring changes to the benzenoid type.

Properties.—Benzoquinone is a yellow crystalline substance, m.p. 117° , with a peculiar smell by which it can be detected. Advantage is taken of its volatility to purify it either by distillation in steam or by sublimation.

The quinones lack the conjugated system characteristic of the benzene ring and hence do not possess the properties of aromatic compounds. They are markedly unsaturated and in fact are $\alpha : \beta$ -unsaturated ketones. Reduction of benzoquinone with mild reducing agents such as sulphurous acid yields hydroquinone, the change from the quinonoid to the aromatic system being accompanied by loss of colour.

The presence of carbonyl groups is shown by the formation of quinone monoxime and dioxime by the action of hydroxylamine hydrochloride (see also p. 514). Phenylhydrazine does not yield a phenylhydrazone, but reduces the quinone to hydroquinone.

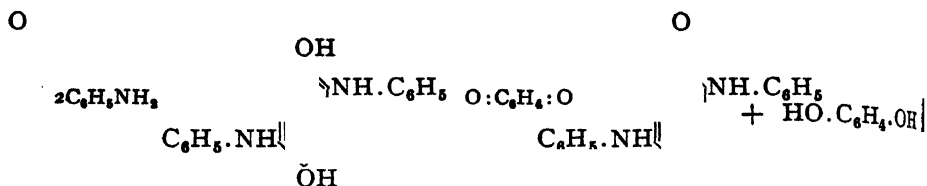
The ethylenic linkages are detected by the usual reagents: hydrogen bromide, hydrogen chloride, bromine and chlorine. It has already been pointed out that benzoquinone is an $\alpha : \beta$ -unsaturated ketone and in consequence certain reactions occur through a 1 : 4-addition intermediate. Thus dry hydrogen chloride gives an unstable dihydrobenzene intermediate which immediately enolises to the stabler aromatic compound, 2-chlorohydroquinone.



Some additions to benzoquinone yield not substituted hydroquinones, but substituted benzoquinones. Aniline, for instance, gives 2 : 5-dianilino-1 : 4-benzoquinone. Probably the reaction proceeds by a double 1 : 4-

¹ J. M. Robertson, *Proc. Roy. Soc.*, 1935, 150, 106.

addition mechanism to give a dianilinohydroquinone, which is oxidised to the dianilino-quinone by another molecule of *p*-benzoquinone.



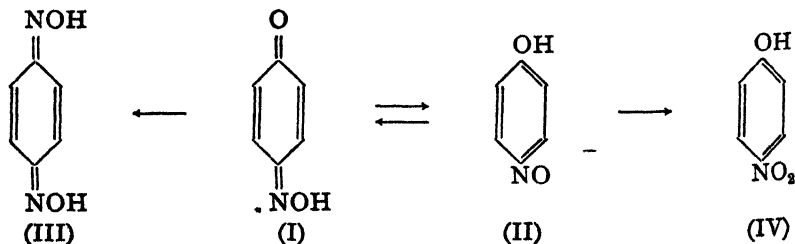
p-Benzoquinone reacts with dienes to give Diels-Alder adducts (p. 451).

The reactions outlined above are characteristic of quinones in general, but substitution and in particular the fusion of benzene rings to the quinone ring modify their properties. Anthraquinone, for instance, is colourless or nearly so and is odourless, and does not participate in the Diels-Alder reaction.

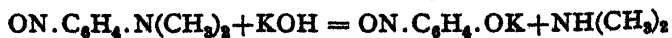
Of the substituted *p*-benzoquinones **chloranil**, tetrachloro-*p*-benzoquinone, $\text{C}_6\text{Cl}_4\text{O}_2$, is the best known and is obtained by oxidising pentachlorophenol by means of nitric acid. It is a useful oxidising agent, and is used both in the manufacture of dyestuffs and for the dehydrogenation of hydrogenated polycyclic hydrocarbons, tetrahydrocarbazoles, etc.

Benzoquinone Oximes or Nitrosophenols

Benzoquinone reacts with one molecule of hydroxylamine hydrochloride in aqueous or ethanolic solution to give benzoquinone monoxime (I). The same product, however, is formed by the action of nitrous acid on phenol thereby suggesting that it is *p*-nitrosophenol (II). The

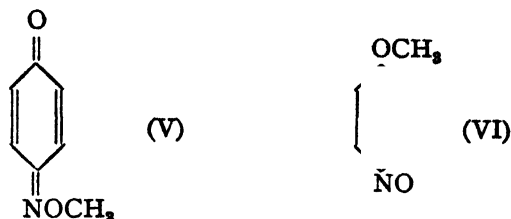


substance is in fact tautomeric. The oxime formula provides the best explanation of the weakly basic character of the compound, and also for its conversion with hydroxylamine hydrochloride into benzoquinone dioxime (III) and on methylation into the methyl ether of benzoquinone monoxime, $\text{O:C}_6\text{H}_4\text{:NOCH}_3$. The nitroso formula is supported by a number of reactions. *p*-Nitrosophenol can be prepared by the method given above or by the alkaline hydrolysis of *p*-nitrosodimethylaniline.



It also gives a green colour in ether solution, and is oxidised by nitric acid to *p*-nitrophenol (IV).

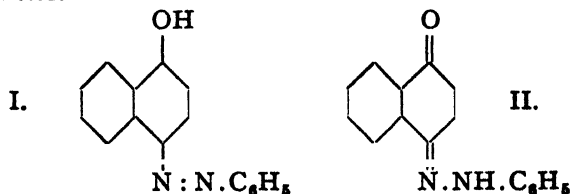
Further insight into the tautomerism of benzoquinone oxime is furnished by its ultra-violet absorption spectrum, which resembles that of the oxime O-methyl ether (V) and differs from that of *p*-nitrosoanisole (VI). This is good evidence that the compound exists predominately



in the oxime form. This method of comparing the ultra-violet spectra of tautomeric substances with those of closely related structures which are "fixed" by methylation is extensively used.

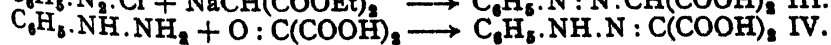
The oximation of substituted benzoquinones figured prominently in the early researches on steric hindrance (p. 448), and Kehrman found that 2:6-disubstituted benzoquinones formed only monoximes, reaction occurring at the unhindered 4-carbonyl group. He further showed that tetrasubstituted benzoquinones formed no oximes due to the blocking of both carbonyl groups.

Tautomerism of another kind is observed in the phenylhydrazones of some quinones, and has been termed *azo-hydrazone tautomerism*. The product (I) obtained by the interaction of diazobenzene chloride and naphthol is identical with (II) prepared from phenylhydrazine and α -naphthaquinone.¹



Only one form has been isolated, but derivatives of both tautomers have been prepared. It has been shown by absorption measurements² that in solvents such as nitrobenzene and acetic acid the quinone form (II) predominates, while in pyridine the hydroxyazo structure (I) obtains. In benzene a mixture of both types is found.

Similarly, R. Meyer found that when diazobenzene chloride is combined with sodio-malonic ester and the product hydrolysed, the substance obtained is identical with that prepared from phenylhydrazine and mesoxalic acid. It may therefore be represented either as a hydrazone IV,



or as an azo-compound III.

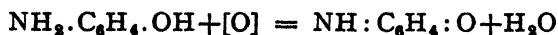
¹ Zincke and Bindewald, *Ber.*, 1884, 17, 3026, Laar, *Ber.* 1885, 18, 648. ² Kuhn and Bar, *Ann.*, 1935, 516, 143.

Quinone-imines

Quinone-imines are formed by replacing one or both of the carbonyl oxygen atoms by the imino-group, NH , or the alkyl- or aryl-imino group, NR . The simplest representatives of these substances, **quinone-imine** (I) or **quinone-diimine** (II) were prepared by Willstätter.



Quinone-imine is obtained by the oxidation of *p*-aminophenol by silver oxide.



It is an exceedingly unstable substance, whose structure follows from its hydrolysis with dilute sulphuric acid to benzoquinone and ammonia, and from its reduction with stannous chloride and hydrochloric acid to *p*-aminophenol. Quinone-imine is obtained in colourless crystals, thereby proving that the quinonoid structure is not necessarily accompanied by colour. As already noted anthraquinone has little or no colour.

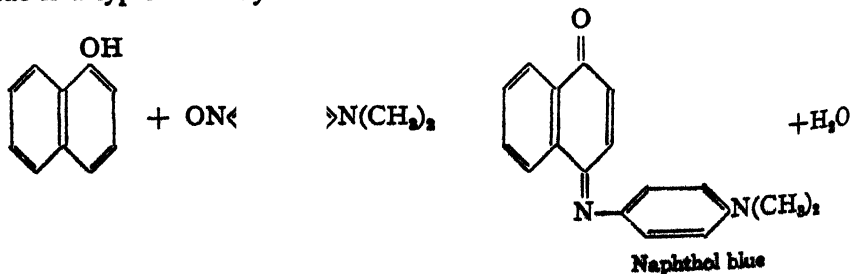
Quinone-diimine is prepared in a similar manner by the oxidation of *p*-phenylenediamine. It is hydrolysed to benzoquinone and ammonia and is reduced to *p*-phenylenediamine. It forms colourless crystals, and is the parent substance of large classes of dyestuffs, chief among which are the indamines and the azines.

Indophenol and Indamine Dyestuffs

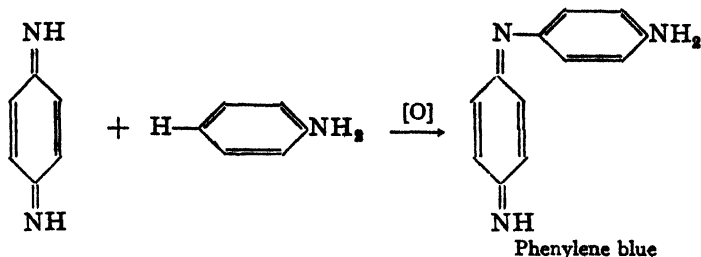
The indophenol and indamine dyestuffs are phenyl-derivatives of quinone-imine and quinone-diimine respectively (see above). They are in fact amino derivatives of structures I and II respectively.



The **indophenols** are obtained by oxidising mixtures of phenols with *p*-diamines or *p*-aminophenols. They are also prepared by condensing *p*-nitrosodimethylaniline with phenols. By the second method α -naphthol is condensed with *p*-nitrosodimethylaniline to yield the most important dye of this class, **Indophenol Blue** or **α -Naphthol Blue**. Naphthol Blue is a typical vat dye.



The indamines are most readily prepared by oxidising mixtures of monoamines and *p*-diamines. In this reaction it may be supposed that quinone-diimine is first produced and then in the course of further oxidation reacts with the *p*-hydrogen atom of the monoamine. Phenylene Blue is thus obtained from aniline and *p*-phenylenediamine.



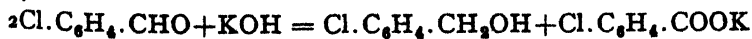
Its structure follows from this synthesis and from the reduction of the dyestuff which gives 4 : 4'-diaminodiphenylamine. The salts are greenish-blue. The corresponding tetramethyl derivative, **Bindschiedler's Green**, is similarly prepared from dimethylaniline and *p*-dimethylaminoaniline. Its salts dissolve to give green solutions.

XI

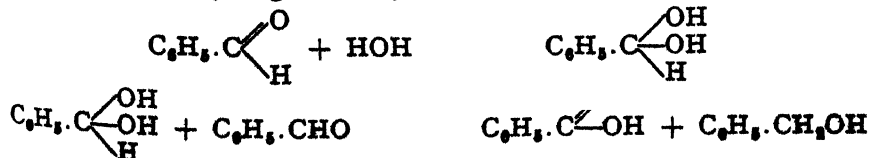
Aromatic Alcohols, Aldehydes and Ketones

When a hydroxyl group is introduced into the side chain of an alkyl benzene, an aromatic alcohol is formed such as benzyl alcohol, $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{OH}$. Compounds of this type may also be regarded as phenyl derivatives of the aliphatic alcohols, which they resemble in most respects. Like the fatty alcohols they may be obtained by heating the corresponding chloro-derivatives with water, by the reduction of aldehydes and ketones, by the action of nitrous acid on amines, and from organo-magnesium halides by combination with aldehydes, ketones or esters. The secondary and tertiary alcohols formed by this last method frequently pass by loss of water into benzene derivatives of olefins (see p. 457).

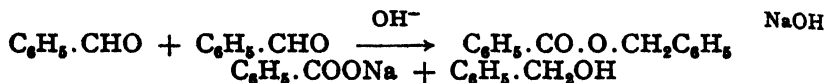
Another useful means of preparing alcohols of this type is to shake the corresponding aldehyde with strong aqueous alkali (*Cannizzaro* reaction).



One attractive and simple theory of the course of this reaction was that benzaldehyde and water reacted to give a hydrated form of benzaldehyde which was then dehydrogenated by a second molecule of aldehyde.



In heavy water, however, the reaction proceeds without the formation of benzyl alcohol containing deuterium in the methylene group. The above mechanism accordingly is not correct. It is possible that the reaction proceeds *via* an intermediate ester such as benzyl benzoate.



Other mechanisms have also been proposed.

Benzyl alcohol, *phenylcarbinol*, $\text{C}_6\text{H}_5\cdot\text{CH}_2\text{OH}$, occurs in the free state and in the form of esters in many ethereal oils. It is generally prepared from benzyl chloride by heating with alcoholic potassium acetate, and hydrolysing the benzyl acetate so obtained or by reduction of benzaldehyde. It is a colourless liquid of faintly aromatic odour, boiling at 206° , and very sparingly soluble in water.

Phenylethyl alcohol, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$, b.p. 219° , is the chief constituent of natural and synthetic rose perfume. It is noteworthy that the isomeric α -phenylethyl alcohol, $\text{C}_6\text{H}_5\cdot\text{CHOH}\cdot\text{CH}_3$, is odourless. It is manufactured by the action of ethylene oxide on benzene in the presence of aluminium chloride (*Friedel-Crafts* reaction)

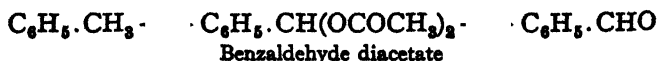


Other alcohols include **cinnamyl alcohol**, $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{CH}_2\text{OH}$, and **salicyl alcohol** (*o*-hydroxybenzyl alcohol or saligenin), $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{OH}$.

Aldehydes

The aromatic like the aliphatic aldehydes are very valuable synthetic reagents and it is not surprising that many methods are available for their preparation, a few of which are given below. In some of these care must be taken to prevent further oxidation of the aldehyde to the carboxylic acid

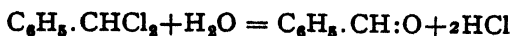
1. *Oxidation of toluene and its derivatives*.—The methyl group may be oxidised to the aldehyde group by chromium trioxide and acetic anhydride. Aldehyde diacetates are formed, thus preventing further oxidation, and are hydrolysed with hydrochloric acid to the aldehydes.



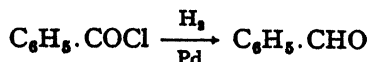
Direct oxidation to the aldehyde is obtained with chromyl chloride (*Etard's reaction*), but its use is limited.

Oxidation of benzyl halides frequently gives yields in the neighbourhood of 65 per cent. In *Sommelet's method* the halide is heated with hexamethylene tetramine in dilute alcohol. The mixture is then acidified and steam-distilled. Oxidation with copper nitrate is also often effective.

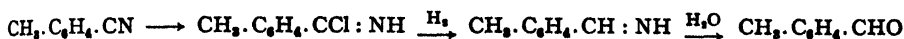
2. *Hydrolysis of benzal chlorides.*—Large quantities of benzaldehyde are manufactured by hydrolysing benzal chloride with water in presence of a catalyst such as iron wire.



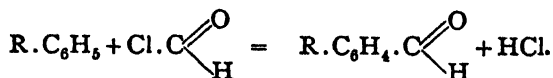
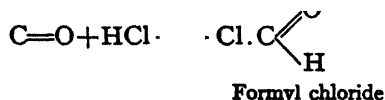
3. *Reduction of carboxylic acid derivatives.*—In the *Rosenmund reduction* acid chlorides with hydrogen and a palladium or nickel catalyst yield aldehydes. A catalytic poison such as thiourea is used to prevent further reduction at the aldehyde stage.



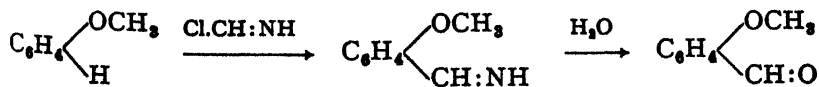
In *Stephen's method* acid nitriles are reduced with stannous chloride, hydrogen chloride, and ether and the product decomposed by steam-distillation.



4. *By the Friedel-Crafts reaction.*—Homologues of benzaldehyde are obtained by the *Gattermann-Koch* reaction by the action of carbon monoxide and hydrogen chloride on toluene, etc., in presence of a mixture of aluminium chloride and cuprous chloride. Formyl chloride is probably formed as an intermediate.



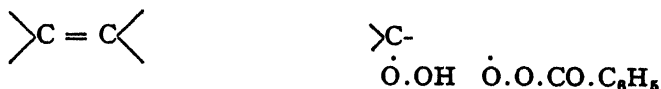
Similarly, by using HCN the aldehyde group may be introduced into phenols, phenolic ethers, or hydrocarbons (*Gattermann* reaction). The method consists in treating the phenolic compound with HCN and HCl, in some cases with the addition of condensing agents such as aluminium chloride or zinc chloride. Hydrogen cyanide first unites with hydrogen chloride to form the chloride of iminoformic acid,¹ which then reacts with the phenol, with elimination of hydrochloric acid, to give an aldolimine. The latter, on heating with dilute acids, is readily converted into the aldehyde itself.



This reaction unlike the *Gattermann-Koch* can be applied to phenols and aromatic ethers.

¹ According to L. E. Hinkel, E. E. Ayling and W. H. Morgan (*J.*, 1932, 2793), the active agent is not the chloride of iminoformic acid but chloromethylene-formamidine, $\text{NH:CH}\cdot\text{N:CHCl}$, produced by union of two molecules of HCN with one HCl. For a simplification of this process, using zinc cyanide in place of hydrogen cyanide, see R. Adams and J. Levine. *J.A.C.S.*, 1923, 45, 2373; 46, 1518.

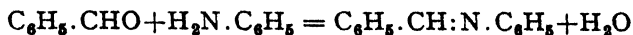
The formation of intermediate free radicals can be detected by "trapping" them by means of suitable ethylenic compounds. In this way a product can be isolated whose formula probably is that shown below.



Benzaldehyde unites with ammonia to give *hydrobenzamide*,



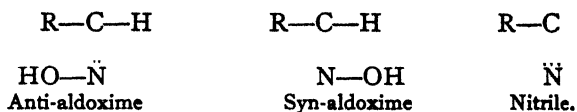
and with aniline to give *benzylidene-aniline*. Compounds of the latter type are known as **Schiff's bases** or **anils**.



The **oxime** of benzaldehyde, $C_6H_5.CH:NOH$, exists in two stereoisomeric forms (see below).

Stereoisomerism of the Aldoximes

Depending on the arrangement of the hydrogen atom and hydroxyl group about the double bond, aldoximes may exist in two isomeric modifications, which are known respectively as the *syn*- and *anti*- forms.



The problem of allotting to a given oxime the appropriate *syn*- or *anti*-configuration proved more difficult than was at first suspected (see general section, p. 53). It is convenient to adopt the suggestion put forward by Brady and to classify these compounds as α - and β -aldoximes, according to the ease with which they may be converted by loss of water into the related nitrile. The α -form on treatment with acetic anhydride at 30° yields an acetyl derivative which on hydrolysis with cold aqueous sodium carbonate regenerates the original oxime. Under the same conditions the β -form loses water and is converted into a nitrile or the corresponding acid. Hantzsch assigned configurations to the two forms by making the plausible assumption that the closer the proximity of the H and OH the more readily will the nitrile be formed. Serious doubts have been thrown on this assumption and it is not now used to determine the configuration of the oximes. More reliable are ring-closure experiments (p. 54) which show that in general α -aldoximes are of the *syn*- and β -aldoximes of the *anti*-configuration.

Aliphatic aldoximes are in general only stable in the β -form, and their α -forms can rarely be isolated. Aromatic aldehydes yield α -aldoximes when treated with hydroxylamine, and these may frequently be transformed into the β -compounds by means of hydrogen chloride.

Thus benzaldehyde yields α -benzaldoxime (*bessynaldoxime*), m.p. 35° , which with hydrochloric acid, sulphuric acid or bromine is converted into β -benzaldoxime (*bensantaldoxime*), m.p. 132° . When the latter is heated the reverse change occurs.

Among nitro- and amino-derivatives of benzaldehyde the *o*-compounds are of importance, and are used in the preparation of various heterocyclic substances.

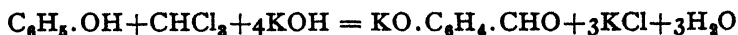
o-Nitrobenzaldehyde, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CHO}$, is formed in about 20 per cent. yield by the nitration of benzaldehyde. It is best obtained by the oxidation of *o*-nitrocinnamic acid, or by oxidising *o*-nitrobenzylaniline and hydrolysing the *o*-nitrobenzylidene-aniline so obtained. It forms colourless needles, m.p. 46° . In sunlight it readily isomerises into *o*-nitrosobenzoic acid, $\text{ON} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$. Its most important reaction is its conversion into indigo. In the presence of caustic soda it combines with acetone to give $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CHOH} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_3$, which readily loses water, yielding *o*-nitrobenzalacetone, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH} \cdot \text{CO} \cdot \text{CH}_3$; on treatment with alkalis the latter immediately parts with acetic acid to form *indigo blue*. *m*-Nitrobenzaldehyde, m.p. 58° , is the chief product of the direct nitration of benzaldehyde. *p*-Nitrobenzaldehyde is obtained by boiling *p*-nitrobenzyl chloride with lead nitrate solution, and forms colourless prisms, m.p. 107° .

On reduction the above nitrobenzaldehydes are converted into the corresponding amino-compounds, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CHO}$, of which the *m*- and *p*-derivatives are used in the preparation of dye-stuffs. *p*-Aminobenzaldehyde is prepared by the action of sodium polysulphides on *p*-nitrotoluene.¹

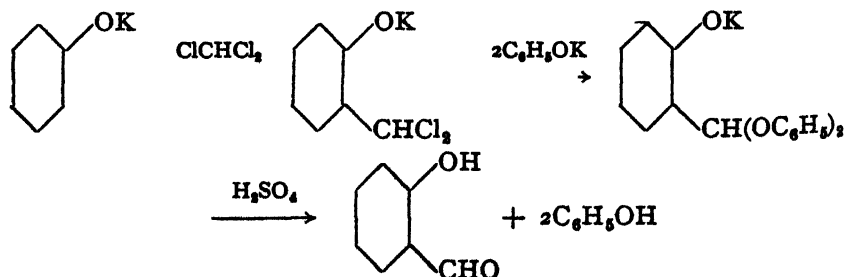
Hydroxy or Phenolic Aldehydes

The hydroxy-aldehydes, a number of which occur in nature, can be prepared by two methods.

1. When a phenol in alkaline solution is treated with chloroform, an aldehyde group is introduced into the *o*- or *p*-position to the phenolic hydroxyl (*Reimer-Tiemann reaction*).



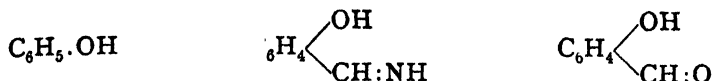
There is good evidence that the reaction proceeds in the following manner²:-



The method is of limited application as considerable quantities of side-products are formed and phenols such as *o*- and *p*-nitrophenol fail to react.

¹ H. H. Hodgson and H. G. Beard, *J.*, 1944, 4. ² D. E. Armstrong and D. H. Richardson, *J.*, 1933, 496.

2. In the presence of hydrogen chloride phenols react with hydrocyanic acid to form *aldo-imines*, which on boiling with dilute acids are readily converted into the corresponding hydroxy-aldehydes. Aluminium chloride or zinc chloride is added in some cases as a condensing agent.



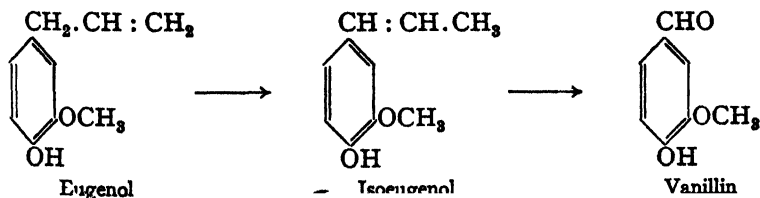
Phenolic aldehydes possess the properties of both phenols and aldehydes.

Salicylaldehyde, *o*-hydroxy-benzaldehyde, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO}$, is found in the volatile oil of *Spiraea ulmaria*, and is prepared by oxidation of the corresponding alcohol saligenin, or together with *p*-hydroxybenzaldehyde by the action of chloroform on an alkaline solution of phenol (*Reimer-Tiemann* method). It is a liquid, b.p. 196° .

Anisaldehyde, *p*-methoxy-benzaldehyde, $\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO}$, is formed by the oxidation of anethole, $\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH} \cdot \text{CH}_3$ (occurring in oil of aniseed, fennel oil and oil of tarragon). It is a colourless liquid, b.p. 248° , which has an aromatic smell.

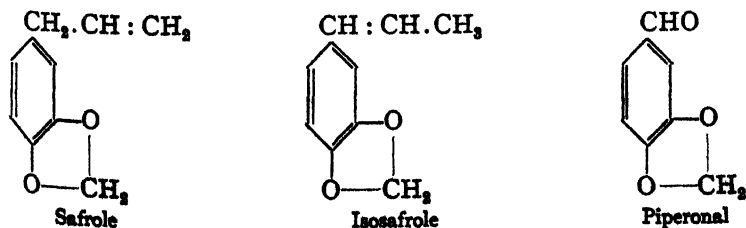
Vanillin, *m*-methoxy-*p*-hydroxy-benzaldehyde, is the active constituent of the vanilla pod, in which it is present to the extent of about 2 per cent. It is the methyl ether of protocatechuic aldehyde, $\text{C}_6\text{H}_3(\text{OH})_2 \cdot \text{CHO}$.

Closely related to vanillin is **eugenol**, which occurs in essential oils. When heated with aqueous potassium hydroxide it undergoes an *allylic rearrangement* to give **isoeugenol** in which the exocyclic double bond is conjugated with the benzene ring. On the industrial scale isoeugenol is acetylated and oxidised to give acetylvanillin. Removal of the acetyl



group by hydrolysis gives vanillin. A new source of vanillin is the lignin-sulphonate waste liquor of American paper mills.

Another double bond shift is observed when safrole, the chief constituent of oil of sassafras, is heated with alkali. Isosafrole is obtained and on oxidation yields piperonal. Piperonal possesses a very pleasant



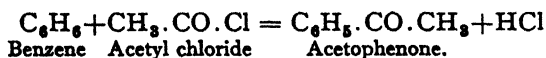
smell resembling that of heliotrope, and is placed on the market as a perfume under the name of heliotropin.

Cinnamic aldehyde, $C_6H_5 \cdot CH:CH \cdot CHO$, is an example of an unsaturated aldehyde. It is found in oil of cinnamon and oil of cassia, to which it imparts the odour of cinnamon. From these sources it may be isolated by means of the sodium bisulphite compound. Synthetically it is obtained by the condensation of benzaldehyde with acetaldehyde (see Cinnamic Acid). It is an oil which boils at 246° .

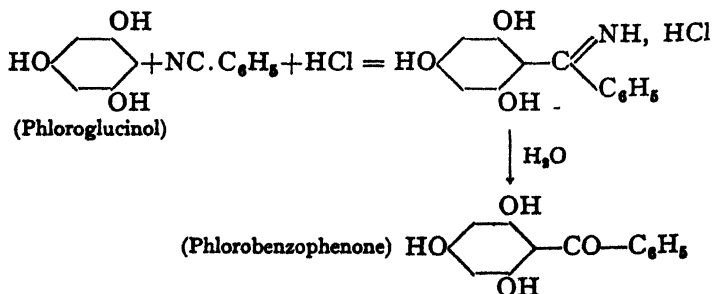
Ketones

If two aromatic radicals are linked together by a CO-group the resulting compound is a purely aromatic ketone, such as benzophenone, $C_6H_5 \cdot CO \cdot C_6H_5$. Ketones containing one aliphatic and one aromatic radical attached to the carbonyl group are termed mixed or fatty-aromatic ketones.

Ketones of this type may be regarded as oxidation products of secondary aromatic alcohols. They are formed by the general methods available for ketones (p. 184), and also by the Friedel-Crafts reaction from acid chlorides and benzene in the presence of aluminium chloride. Better yields are frequently obtained if acid anhydrides are substituted for acid chlorides.



Aromatic hydroxy-ketones may be prepared by the method of *Houben* and *Hoesch*¹ from polyhydric phenols. The latter, especially those containing hydroxyl groups in the *m*-position to each other, readily react with aliphatic or aromatic nitriles in the presence of hydrogen chloride to form ketiminochlorides, which on boiling with water yield the corresponding ketones, *e.g.*,



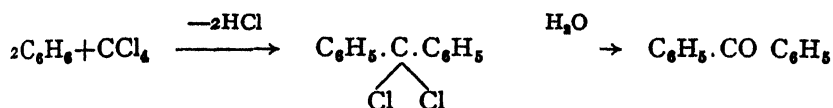
This reaction may be regarded as an extension of *Gattermann's* aldehyde synthesis (p. 519).

Aromatic ketones undergo the same typical reactions as those of the fatty series. Aliphatic-aromatic ketones may be reduced to hydrocarbons by use of *Clemmensen's* method (*q.v.*).

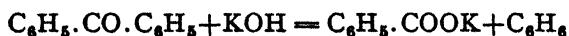
¹ K. Hoesch, *Ber.*, 1927, 60, 389, 2537; J. Houben, *Ber.*, 1928, 61, 1597.

Acetophenone, *phenyl methyl ketone*, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$, is prepared by the interaction of acetic anhydride and benzene in the presence of aluminium chloride (Friedel-Crafts reaction). It crystallises in large plates, m.p. 20° , b.p. 202° , and is used as a hypnotic under the name of *hypnone*. When warmed with halogens, acetophenone undergoes substitution in the side chain. **Phenacyl bromide**, *ω-bromoacetophenone*, m.p. 50° , prepared in this way, is a lachrymatory compound which is useful in synthetic work.

Benzophenone, *diphenyl ketone*, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{C}_6\text{H}_5$, b.p. 307° , may be obtained by the usual methods and is best prepared by the Friedel-Crafts reaction, the method by which it is manufactured, benzene being made to react with an excess of carbon tetrachloride in the presence of aluminium chloride.



It exists in two solid modifications, a stable form, m.p. 49° and a labile form, m.p. 27° . The latter readily changes into the former. Benzophenone on reduction yields the secondary alcohol benzhydrol, $\text{C}_6\text{H}_5\cdot\text{CHOH}\cdot\text{C}_6\text{H}_5$, m.p. 68° , and finally *diphenylmethane*, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{C}_6\text{H}_5$ (see p. 549). When fused with potash it decomposes into benzene and benzoic acid,



In its other chemical properties, *e.g.* in its behaviour towards hydroxylamine, phenyl hydrazine and phosphorus pentachloride, it completely resembles the aliphatic ketones. When treated in alcoholic solution with dry hydrogen chloride and hydrogen sulphide, benzophenone yields thiobenzophenone $(\text{C}_6\text{H}_5)_2\text{CS}$, a deep violet crystalline compound, m.p. 51° to 52° .

Propiophenone, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_3$, is manufactured by the Friedel-Crafts method.

p-**Tetramethyl-diamino-benzophenone**, *Michler's ketone*, is prepared by the action of carbonyl chloride on dimethylaniline.



By further condensation with dimethylaniline it yields *Crystal Violet*, (p. 559). On reduction it passes into the corresponding alcohol *p*-tetramethyl-diamino-benzhydrol, $\text{CHOH}[\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2]_2$, which is also employed in the preparation of dye-stuffs.

Ketenes.—The ketenes (see p. 201) have already been described. **Diphenyl-ketene**, $(\text{C}_6\text{H}_5)_2\text{C}:\text{CO}$, the first member of the group to be prepared, was obtained by Staudinger from diphenyl-chloracetyl chloride

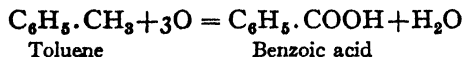
$(\text{C}_6\text{H}_5)_2\text{CCl.COCl}$, by the removal of chlorine with zinc. Diphenylketene is a highly coloured and strongly unsaturated substance. It is very reactive and undergoes oxidation in air.

XII

Aromatic Carboxylic Acids

Aromatic acids are found free and in the combined state in many resins and balsams. They may be prepared by methods similar to those used for aliphatic acids, and by a number of special reactions, of which the following are the most important.

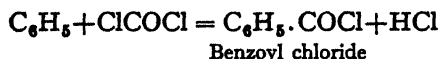
1. By oxidation of aromatic hydrocarbons and other benzene derivatives containing side chains, when the latter are converted into carboxyl groups.



A compound with one side chain attached to the nucleus oxidises to a monocarboxylic acid, while the presence of two or three side chains leads to the formation of di- or tricarboxylic acids respectively.

2. In a similar manner to aliphatic acids by the hydrolysis of nitriles. The latter are most conveniently prepared from diazonium salts (see p. 478), by the interaction of benzene-sulphonates with potassium cyanide or by refluxing bromo-compounds with cuprous cyanide.¹

3. Acid chlorides can be prepared by the action of phosgene or oxalyl chloride on benzene and its derivatives in the presence of aluminium chloride (Friedel-Crafts).



4. Dry carbon dioxide reacts with Grignard reagents to form carboxylic acids.

Aromatic carboxylic acids are usually solid crystalline compounds which are sparingly soluble in water. Like the fatty acids they form chlorides, amides, esters and other derivatives. Further, by substitution in the benzene ring there may be obtained nitro-, amino-, chloro- and other derivatives which are dealt with in more detail later.

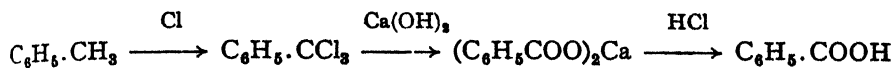
I.—MONOBASIC ACIDS

1. Benzoic Acid and its Homologues

Benzoic acid, $\text{C}_6\text{H}_5.\text{COOH}$, is found in gum benzoin, in Peru and Tolu balsams, and is present in the form of hippuric acid in the urine of horses. Originally it was prepared by heating gum benzoin, when

¹ For experimental details see M. S. Newman, *Organic Syntheses*, 21, 89.

the acid sublimes, or from hippuric acid, which on boiling with mineral acids is hydrolysed to glycine and benzoic acid. It is still obtained from gum benzoin for pharmaceutical purposes ("acidum benzoicum ex resina"), but otherwise is prepared almost exclusively from toluene. The latter is first converted into benzo-trichloride by treatment with chlorine at the boiling-point, and this is hydrolysed with milk of lime to give calcium benzoate, from which benzoic acid is precipitated by the addition of hydrochloric acid and purified by recrystallisation from water.

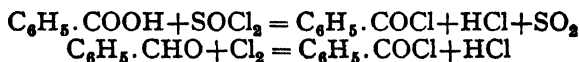


Benzoic acid is now prepared in large quantities by catalytic oxidation of toluene with air.

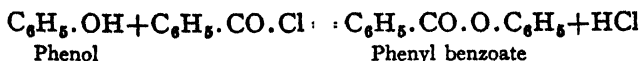
Benzoic acid crystallises in colourless glistening plates, and has a faint aromatic smell. It melts at 121° , boils at 250° , very readily sublimes and is volatile in steam. Although only sparingly soluble in cold water, it dissolves readily in the hot liquid, and also in alcohol and ether.

Salts of ammonia and the alkali metals are soluble in water, but most of the others are insoluble. When heated with lime, benzoic acid is decomposed into benzene and carbon dioxide. It is employed in medicine and in the manufacture of aniline blue.

Benzoyl chloride, $\text{C}_6\text{H}_5\cdot\text{COCl}$, is prepared by warming the acid with phosphorus pentachloride or preferably thionyl chloride or by the action of chlorine on benzaldehyde.



It is a colourless liquid, b.p. 199° , with an unpleasant, pungent smell. In behaviour it resembles acetyl chloride, though differing in its greater stability as shown by the slowness with which it is attacked by water. Benzoyl chloride is frequently used as a means of introducing the benzoyl group, $\text{C}_6\text{H}_5\cdot\text{CO}$ —, into hydroxy-, amino- and imino-compounds. This is usually effected by shaking the substance with benzoyl chloride and excess of dilute sodium hydroxide until the smell of the former has disappeared (*Schotten-Baumann reaction*), e.g.,



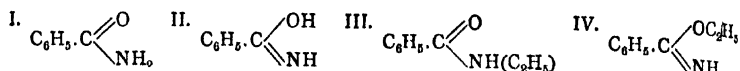
In many cases it is better to use sodium carbonate or pyridine in place of sodium hydroxide.

Ethyl benzoate, $\text{C}_6\text{H}_5\cdot\text{COOC}_2\text{H}_5$, prepared by the usual methods, is a pleasant-smelling liquid of boiling-point 213° .

It has already been mentioned (p. 448) that benzoic acids with substituents in both ortho positions are very resistant to esterification with alcohols and hydrochloric acid. Esterification in such cases may be effected by other methods such as interaction of alcohols with acid chlorides. A case of particular interest is that of 2 : 6-dimethylbenzoic acid, which

can be esterified by dissolving it in 100 per cent. sulphuric acid and pouring the solution into alcohol.¹ Immediate esterification is obtained. The acid is not esterified by the Fischer-Speier method.

Benzamide, $C_6H_5 \cdot CO \cdot NH_2$, is obtained by the action of ammonia or ammonium carbonate on benzoyl chloride. It crystallises in white plates, m.p. 130° , b.p. 288° . When silver benzamide is treated with ethyl iodide it forms the benzimino-ether (IV) instead of the expected ethyl benzamide (III). Hence benzamide is tautomeric and may react according to either of the formulæ I or II.

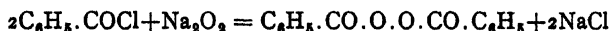


On the other hand, ethyl benzimino-ether (IV) isomerises into ethyl benzamide (III) on being heated to 100° with ethyl iodide.

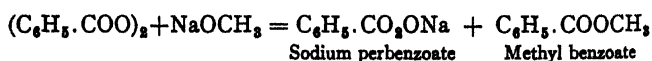
Hippuric acid, benzoyl-aminoacetic acid, $C_6H_5 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$, m.p. 187° , has been mentioned on p. 244. It occurs in the urine of herbivorous animals, and may be prepared by the benzoylation of glycine. On boiling with alkalis or acids it is hydrolysed into benzoic acid and glycine.

Benzonitrile, $C_6H_5 \cdot CN$, is best prepared by heating potassium benzene sulphonate with potassium cyanide. It is an oil, b.p. 191° with a smell like bitter almonds. In its properties it resembles the fatty nitriles.

Dibenzoyl peroxide, $C_6H_5 \cdot CO \cdot O \cdot O \cdot CO \cdot C_6H_5$, is prepared by shaking benzoyl chloride with an aqueous solution of sodium peroxide.



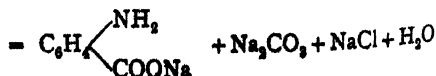
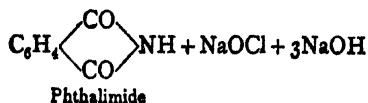
Dibenzoyl peroxide is converted into the sodium salt of perbenzoic acid by the action of sodium methoxide.



This is the best method for the preparation of perbenzoic acid.

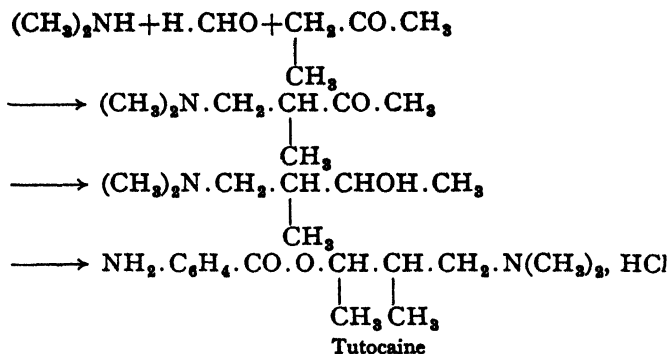
Substituted Benzoic Acids.

Among the *aminobenzoic acids*, which possess basic as well as acidic character (see glycine), the most important is the ortho-compound, **anthranilic acid**, m.p. 145° , first obtained by fusing indigo with alkali. It is an important intermediate product in the technical preparation of indigo (described later), for which purpose it is produced in large quan-

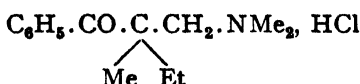


¹ M. S. Newman, *J.A.C.S.*, 1941, 63, 2431.

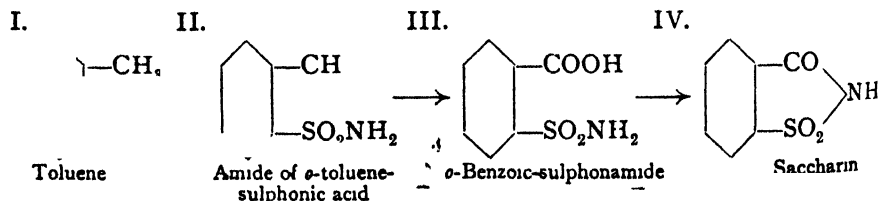
Mannich base (p. 177) from dimethylamine, formaldehyde, and methyl ethyl ketone.



Another well-known local anæsthetic is *Stovaine*,



The three sulphobenzoic acids, $\text{SO}_3\text{H} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$, are obtained from the three toluene sulphonic acids by oxidation with potassium permanganate. *m*-Sulphobenzoic acid, accompanied by a little *p*-compound, is the chief product of the sulphonation of benzoic acid. The *imide* of *o*-sulphobenzoic acid (IV) is 500 times sweeter than sugar, and is sold as a sugar substitute under the name of **saccharin**. It is manufactured from toluene (I), which by sulphonation gives *o*-toluene-sulphonic acid, the amide of which (II) yields saccharin on oxidation. The *o*-benzoic-sulphonamide (III) formed in the last stage immediately loses water :



Saccharin itself is only sparingly soluble in water, but owing to the presence of the imido-group it possesses acidic properties, and forms salts.

The sodium salt, $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{SO}_2 \diagup \end{array} \text{NNa}$, dissolves readily in water and is about 400 times sweeter than sugar.

Homologues of Benzoic Acid and their Derivatives

Homologues of benzoic acid may be of two types, namely alkylated benzoic acids, $\text{R} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$, and phenyl-substituted aliphatic acids, $\text{C}_6\text{H}_5 \cdot \text{R} \cdot \text{COOH}$. The former resemble benzoic acid more closely than

the latter. Phenylacetic acid, m.p. 86° , is prepared by acting on benzyl chloride with potassium cyanide and hydrolysing the resulting benzyl cyanide.



It is oxidised by selenium dioxide to *benzoyl-formic acid*, $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{COOH}$.

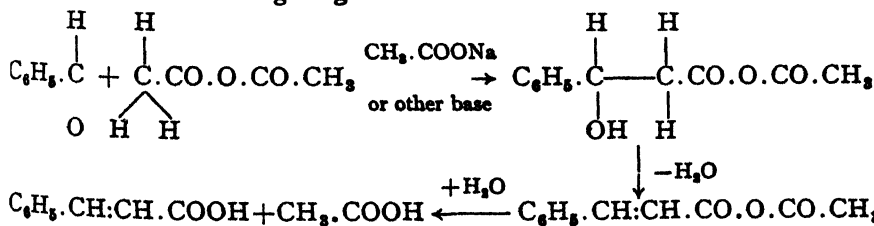
Mandelic acid, $\text{C}_6\text{H}_5\cdot\text{CHOH}\cdot\text{COOH}$, contains an asymmetric carbon atom, and hence occurs in two optically active forms and an inactive racemic form. The latter, m.p. 118° , may be obtained by the addition of HCN to benzaldehyde, and hydrolysing the cyanhydrin so produced by means of hydrochloric acid. It can be resolved into the active acids (m.p. 133°) by recrystallisation of the cinchonine salts. (—)-*Mandelic acid*, the naturally occurring form, is prepared by warming amygdalin with fuming hydrochloric acid.

Phenylalanine, β -*phenyl- α -amino-propionic acid*, $\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{COOH}$, m.p. 283° to 284° , occurs with asparagine in the embryo of vetch; the L-form is produced by the putrefaction or hydrolysis of proteins such as silk fibroin, oxyhaemoglobin and casein. The racemic acid is prepared by Erlenmeyer's azlactone method (p. 236).

2. Monobasic Unsaturated Acids

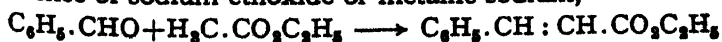
Cinnamic acid, $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{COOH}$, is found free or as an ester in Peru and Tolu balsams and in storax. It can be prepared by a variety of methods.

1. By *Perkin's reaction*, in which benzaldehyde is condensed with acetic anhydride in the presence of sodium acetate. The reaction possibly proceeds in the following stages ¹:



Perkin's reaction may be applied to the synthesis of numerous unsaturated acids and their substituted derivatives. In the above example benzaldehyde may be replaced by its homologues, its halogen- or nitro-substitution products, etc., and acetic anhydride by various other anhydrides.

2. By the *Claisen condensation*, using benzaldehyde and acetic ester in the presence of sodium ethoxide or metallic sodium,



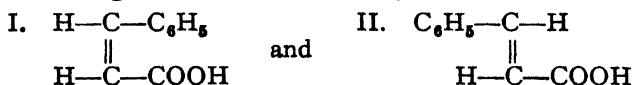
This reaction is also of general application.

¹ C. R. Hauser and D. S. Breslow, *J.A.C.S.*, 1939, 61, 786-793. Reaction also occurs if sodium acetate is replaced by certain amines or by potassium carbonate (Kalmn, *Helv. Chim. Acta*, 1928, 11, 977).

3. Technically it is prepared from benzal chloride by heating with sodium acetate.

Cinnamic acid possesses the properties characteristic of ethylene derivatives, adding on bromine and hydrogen, and decolorising alkaline permanganate solution.

The cinnamic acid of the laboratory, m.p. 133° , is the *trans*-acid (II) and is converted into the *cis*-form (I) by irradiating a benzene solution with ultra-violet light. The *cis*-acid may also be obtained by reducing



phenylpropionic acid with hydrogen and a palladium catalyst. The two cinnamic acids are each polymorphous (p. 64). The *trans*-acid exists in two forms, both with the m.p. 133° , while the *cis*-acid is trimorphic and can be obtained in forms m.p. 42° , 58° , and 68° . Any one of the three forms can be changed into another merely by melting and seeding out the cooled melt with a crystal of the desired form (Biilmann).

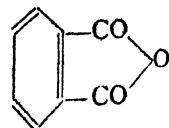
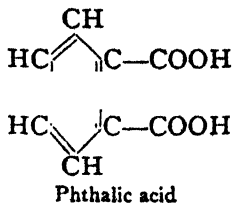
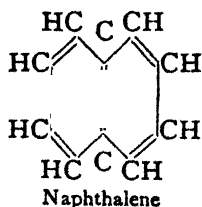
o-Nitrocinnamic acid, m.p. 240° , is of interest in connection with the synthesis of indigo. It is formed together with the *p*-compound by treating cinnamic acid with concentrated nitric acid.

When the dibromide of *o*-nitrocinnamic acid is boiled with alcoholic potash it yields *o*-nitrophenyl-propionic acid, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C} : \text{C} \cdot \text{COOH}$, which with reducing agents such as glucose and potassium hydroxide, hydrogen sulphide, or ferrous sulphate, is converted into indigo blue.

II.—POLYBASIC ACIDS

Polybasic aromatic acids may contain the carboxyl groups entirely in the nucleus, entirely in side chains (aryl-substituted fatty acids), or partly in the nucleus and partly in side chains. Chief among them, from the theoretical as well as the practical standpoint, are the dibasic phthalic acids. Reference is frequently made to these acids in determining the position of side chains in a benzene derivative, and the *o*-acid, ordinary phthalic acid, is also employed in the preparation of various dye-stuffs.

Phthalic acid, *benzene-o-dicarboxylic acid*, $\text{C}_6\text{H}_4(\text{COOH})_2$, is the final oxidation product of a number of benzene derivatives containing two organic side chains in the ortho-position. It is used in large quantities



Phthalic anhydride.

in the manufacture of indigo and other dyes, for which purpose it used to be obtained by heating naphthalene with fuming

sulphuric acid, with the addition of mercuric sulphate as catalyst. During the oxidation sulphur trioxide becomes reduced to sulphur dioxide, $\text{SO}_3 = \text{SO}_2 + \text{O}$, which is recovered and converted into the trioxide.

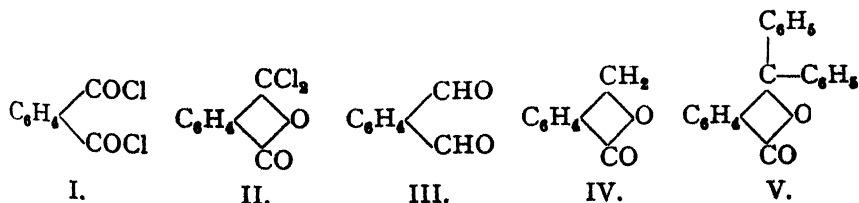
By the more recent process of Wohl (1916) and Gibbs (1917) pure phthalic anhydride is prepared technically in almost quantitative yield by passing naphthalene vapour and air over vanadium pentoxide at 450° to 520° .

Considerable quantities of the acid are now prepared in the United States by the vapour phase oxidation of *o*-xylene obtained in 85-90 per cent. purity from petroleum by the hydroforming process.

Phthalic acid crystallises in glistening plates, which are moderately soluble in hot water. When heated it loses water and passes into the anhydride. It is readily esterified to *dimethyl phthalate*, widely used as an insect repellent (midges and mosquitoes) and plasticiser.

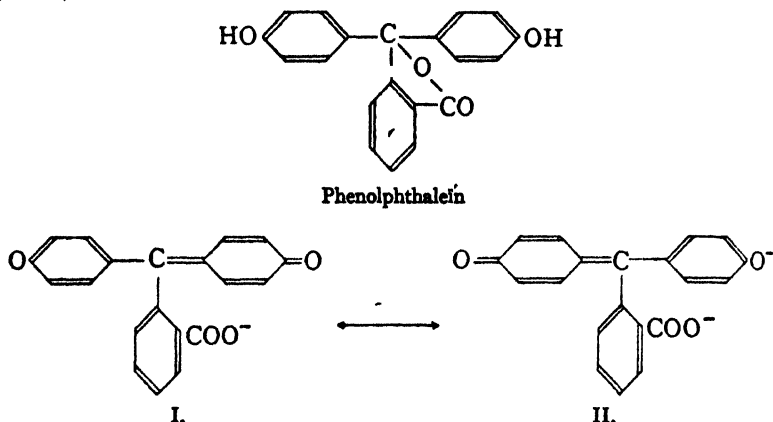
Phthalic anhydride forms long needles, m.p. 128° , b.p. 285° . It is used extensively for the manufacture of anthraquinone, anthranilic acid, indigo, butyl phthalate (nitrocellulose plasticiser), etc. With phosphorus pentachloride it yields *phthaloyl chloride*, which exhibits *ring-chain isomerism* by reacting chemically in both structures I and II. For instance phthaloyl chloride with benzene and aluminium chloride forms both anthraquinone and diphenylphthalide (phthalophenone) (V). With hydrazine it reacts in form I to give a cyclic hydrazide, whereas with zinc dust and acetic acid it reacts in form II to yield *phthalide* (IV), a carbocyclic lactone. Final proof of the existence of the two tautomeric forms is afforded by their isolation. The symmetrical form (I) is prepared by the action of phosphorus pentachloride on phthalic anhydride and on treatment with aluminium chloride is transformed into the unsymmetrical form (II). This type of ring-chain isomerism is observed in the diacid halides of those dicarboxylic acids whose carboxylic groups are in close proximity.

Phthalaldehyde (III) and phthalide (IV) also furnish examples of ring-chain tautomerism.



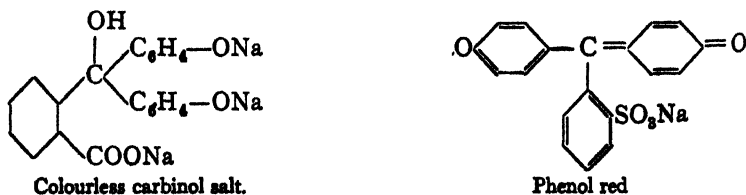
Phthalic anhydride condenses with phenols to form triphenyl-methane dye-stuffs. The reaction proceeds by the *p*-hydrogen atoms of two molecules of phenol uniting with a carbonyl oxygen atom of anhydride to give water. The simplest of these compounds is *phenolphthalein* (formula, p. 534), which is prepared by heating phthalic anhydride and

phenol at 120° in the presence of sulphuric acid. It forms colourless crystals, and is a lactone which dissolves in alkali to give an intense red solution from which the compound is precipitated in the colourless state by the addition of acids. On this colour change depends the use of phenolphthalein in volumetric analysis. The change of colour from colourless to red is assumed to coincide with fission of the lactone ring accompanied by formation of the disodium salt (formula I, anion alone depicted).



The formation of colour is attributed to two factors: (1) the formation of a quinonoid ring in the molecule, and (2) the fact that while the colourless lactone exhibits resonance of the benzene ring only, the disodium salt shows additional resonance between structures I and II. If a considerable excess of alkali is added the solution becomes colourless, probably due to the production of a triphenylcarbinol trisodium salt formed by direct union of the disodium salt with sodium hydroxide (see formula below).

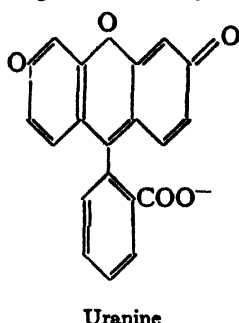
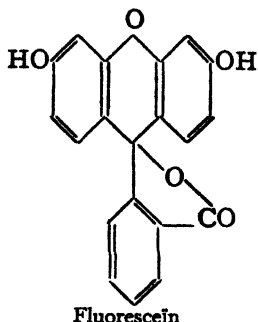
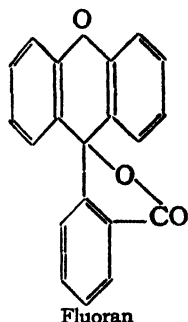
Sulphaphthaleins are now widely used for titrations and supply



indicators over the pH range 1.2-9.0. An example of a sulphaphthalein is *Phenol Red* (see formula).

If, in the above condensation a *meta*-dihydric phenol is used in place of phenol, a phthalein is first formed from which water is split out to form a *fluoran* derivative or *fluorescein*. The parent compound *fluorescein* is formed by fusing resorcinol with phthalic anhydride in the presence of sulphuric acid or zinc chloride. It is a dark yellow crystalline substance

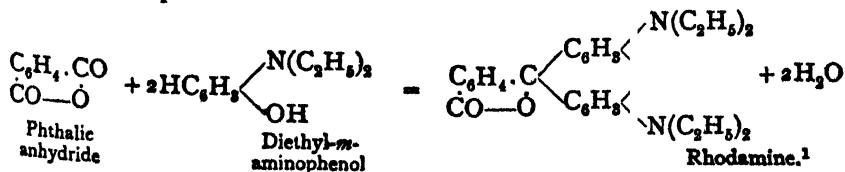
which dissolves in alkalis giving solutions with a magnificent green fluorescence. This characteristic property of fluorescein is used as a test for *meta*-dihydric phenols (p. 509) as well as for phthalic anhydride.



The fluorescence is due to the formation of the disodium salt (the *Uranine* of commerce), the anion of which like that of phenolphthalein contains a quinonoid ring and resonates strongly. Fluorescein is the starting-point in the preparation of most of the important dye-stuffs derived from phthalic acid. When treated with bromine, substitution occurs in the resorcinol groups with the formation, for example, of *tetrabromofluorescein*, $C_{20}H_8O_5Br_4$, the potassium salt of which is used industrially under the name of *eosin*. In a weakly acid bath the latter dyes wool and silk fine shades of red.

In place of phthalic anhydride its di- and tetrachloro-derivatives may also be fused with resorcinol, with the production of fluoresceins which are chlorinated in the phthalic acid group. From these, by bromination and iodination, are prepared the dye-stuffs known as *Phloxines* and *Rose Bengals* respectively. The dyes obtained from chlorinated phthalic acids are distinguished from derivatives of ordinary fluorescein by a somewhat bluer shade of red, and are employed particularly in dyeing silk. *Gallein*, prepared by fusing together phthalic anhydride and pyrogallol, is a violet dye, which with concentrated sulphuric acid at 200° yields *Coerulein*. The latter dyes green and is a derivative of phenylanthracene.

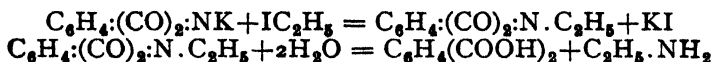
The **Rhodamines**, another group of dyes, are phthaleins of *m*-aminophenol and its *N*-alkylated derivatives. They are obtained by condensing phthalic anhydride with *m*-aminophenols, and are among the finest of the red dyes. The rhodamines may be regarded as diamino-derivatives of fluorane. Commercial rhodamine consists mainly of the phthalein of diethyl-*m*-aminophenol :



¹ In the rhodamines the NH_2 or $\text{N}(\text{Alk})_2$ group occupies the *p*-position to the carbon atom of the phthalic residue.

Phthalimide, $\text{C}_6\text{H}_4 \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{NH}$, m.p. 238° , can be prepared by the

action of ammonia on phthalic anhydride. It is used, on the one hand, for the technical preparation of anthranilic acid, and on the other for the production of primary aliphatic amines and primary amino-acids by Gabriel's method (see p. 176). The synthesis of primary amines by this method is effected as follows.¹ Phthalimide reacts with alcoholic potash to form *potassium phthalimide*, $\text{C}_6\text{H}_4 : (\text{CO})_2 : \text{NK}$, which when treated with alkyl halides exchanges the metallic atom for an alkyl radical. The alkyl phthalimide so obtained may be decomposed by heating with fuming hydrochloric acid, to give phthalic acid and a primary amine. The latter is obtained free from any admixed secondary and tertiary amines.



A remarkable series of complex pigments has recently been prepared from phthalimide and from phthalonitrile. These are described later in connection with *Monastral Blue*.

Isophthalic acid, *benzene-m-dicarboxylic acid*, $\text{C}_6\text{H}_4(\text{COOH})_2$, m.p. 348° , results from the oxidation of benzene derivatives containing two carbon chains in the *m*-position, and may be prepared by oxidising *m*-xylene with calcium permanganate. A derivative of isophthalic acid has already been mentioned in *uvitic acid* (see p. 274).

Terephthalic acid, *benzene-p-dicarboxylic acid*, $\text{C}_6\text{H}_4(\text{COOH})_2$, is manufactured by the oxidation of *p*-xylene. The acid is of importance for the manufacture of terylene (p. 882).

III.—PHENOLIC ACIDS

Aromatic hydroxy acids containing the hydroxyl group in an aliphatic side chain resemble in many ways the hydroxy-acids of the fatty series, and certain representatives of these aromatic alcohol-acids have already been mentioned. On the other hand, aromatic acids in which a hydroxyl group is attached to the nucleus combine the properties of an acid with those of a phenol, and are therefore described as phenolic acids. They may be obtained by a number of methods, of which the following are the most important.

1. By the action of carbon dioxide on alkali phenoxides at high temperature (see Salicylic Acid).
2. By the interaction of carbon tetrachloride and phenols in alkaline solution :



The carboxyl group tends to assume the *p*-position to the hydroxy group.

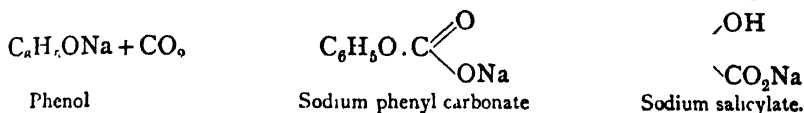
¹ For valuable improvements in this method see Ing and Manske, *J.*, 1926, 129, 2348.

Monohydroxy-monocarboxylic Acids

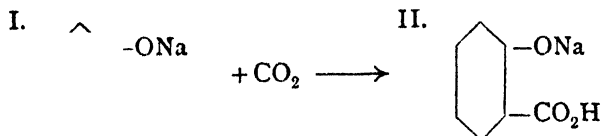
1. Hydroxy-benzoic Acids

Salicylic acid, *o*-hydroxy-benzoic acid, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$, m.p. 155° , occurs in the form of its methyl ester as the chief constituent of oil of wintergreen, from which it is isolated for therapeutic purposes. The corresponding phenolic alcohol, *saligenin* (see index), is a component of the glucoside salicin. Salicylic acid is prepared technically by heating sodium phenoxide with carbon dioxide under pressure at about 140° (*Kolbe's method*).

For a long time this reaction was assumed to take the following course :



but as a result of later investigation it appears that the simplest explanation is the correct one, the sodium phenate (I) combining directly with carbon dioxide, at the temperature employed, to form the sodium derivative of phenol-*o*-carboxylic acid (II).



Free salicylic acid is precipitated by the addition of mineral acid and recrystallised from hot water. In aqueous or alcoholic solution it gives a violet coloration with ferric chloride. It is employed as an antiseptic, particularly in the preservation of food, and is used in the preparation of dye-stuffs. Formerly it was used medicinally in cases of rheumatism, but it produces certain undesirable after-effects and has now been displaced by derivatives such as *aspirin* (acetyl salicylic acid), $\text{CH}_3\text{CO} \cdot \text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$ (m.p. 128°), having a milder action.

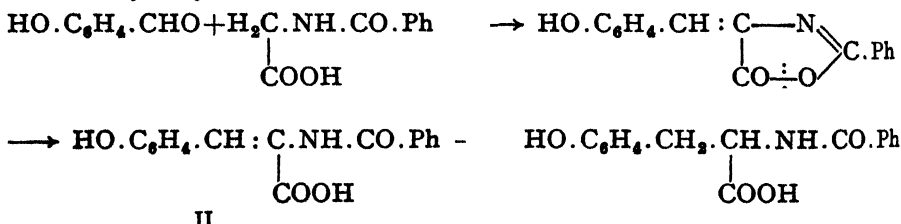
When salicylic acid is treated with an equivalent proportion of a phenol in the presence of phosgene or phosphorus oxychloride, esters are obtained. Thus *phenyl salicylate*, usually termed *salol*, $\text{C}_6\text{H}_4(\text{OH})\text{COOC}_6\text{H}_5$, is prepared by the action of phosgene on a mixture of phenol and salicylic acid. It melts at 42° , and is used as an antiseptic. Salicylate therapy was known to Hippocrates and Galen in the form of the application of willow leaves. Since its introduction, synthetic salicylic acid has been increasingly used in the manufacture of derivatives, and the United States production of the acid is about 6000 tons per annum.

Meta- and *para*-hydroxy-benzoic acids, m.p. 200° and 210° respectively, can be prepared from the corresponding amino- and halogen-substituted benzoic acids. The acids are of little importance but some of their derivatives are of interest. *Methyl p*-amino-*m*-hydroxy-benzoate, m.p. 121° , is used as a local anæsthetic (under the name of *orthoform*), as is also the *m*-amino-*p*-hydroxy-derivative (*new orthoform*). *p*-Amino-salicylic acid is now used in the treatment of tuberculosis.

p-Methoxy-benzoic acid, anisic acid, $\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{COOH}$, m.p. 185° , is formed by the oxidation of oil of aniseed, and may be prepared from *p*-hydroxy-benzoic acid by methylation with methyl iodide and alkali, or from *p*-bromo-anisole by the Grignard reaction, using magnesium and carbon dioxide.

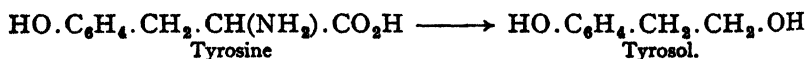
2. Monobasic Phenolic Acids with Carboxyl in the Side Chain, and the Coumarins

L-Tyrosine, *p*-hydroxyphenyl-alanine, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$, occurs in the (—)-form (m.p. $314\text{--}318^\circ$) in old cheese, the berries of the elder, the spleen, the pancreatic gland, and in diseased liver. It occurs in most proteins but not in gelatine and is detected by Millon's reagent. *r*-Benzoyltyrosine can be conveniently obtained by the method of Erlenmeyer, Jr. *p*-Hydroxybenzaldehyde is condensed with hippuric acid in acetic anhydride to give the azlactone (I) which on hydrolysis yields *p*-hydroxy- α -benzoylaminocinnamic acid (II). Reduction of this acid gives *r*-benzoyltyrosine, from which *r*-tyrosine is obtained by acid or alkaline hydrolysis.



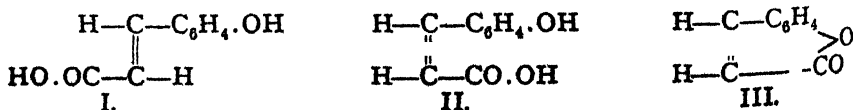
A physiologically important derivative of tyrosine is the hormone, *thyroxine*.

Tyrosol, or *p*-hydroxyphenyl-ethyl alcohol, is produced by the fermentation of tyrosine with sugar and compressed yeast.



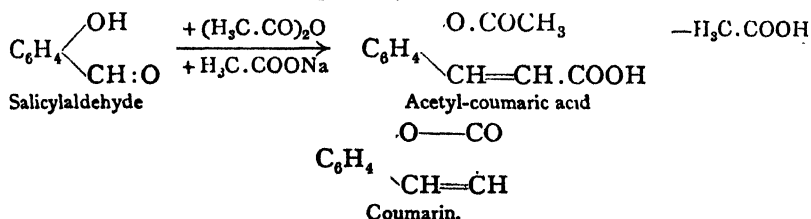
Tyrosol crystallises in small, colourless needles, m.p. 93° and b.p. about 310° . It is a normal product of the protein metabolism of yeast and hence is a by-product of all kinds of yeast fermentations, being found in the majority of fermented beverages, particularly in beer and wine.

***o*-Hydroxy-cinnamic acid**, $\text{HO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$, exists in two isomeric forms, distinguished as **coumarinic acid** and ***o*-coumaric acid** respectively. These acids bear the same relationship to one another as maleic and fumaric acids. In coumarinic acid (II) the groups $\text{HO} \cdot \text{C}_6\text{H}_4\text{—}$ and —COOH lie on the same side of the molecule (*cis*-form), and in coumaric acid (I) they are on opposite sides (*trans*-form).



The chief difference between these compounds is that coumarinic acid in aqueous or alcoholic solution is only stable in the form of its salts, and when liberated in the free state passes at once into the lactone, *coumarin* (III). On the other hand, *o*-coumaric acid is readily obtained in the free state. *o*-Coumaric acid occurs in *melilotus officinalis*, and may be prepared from *o*-amino-cinnamic acid by way of the diazo-compound, or from coumarin by boiling with sodium ethoxide. The coumarin nucleus is found in nature in certain hydroxycoumarins (see p. 540) and furano-coumarins in which the coumarin nucleus is fused to a furan ring.

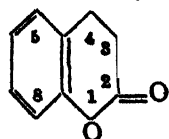
Coumarin (formula III above) is responsible for the perfume of the woodruff (*Asperula odorata*), and occurs also in melilot and in the Tonquin bean. W. H. Perkin, Sen., found that coumarin when fused with potassium hydroxide gave salicylic and acetic acids. This led him to synthesise coumarin, the structure of which was then unknown, by heating salicyl aldehyde with sodium acetate and acetic anhydride. In this way the famous Perkin synthesis (p. 531) was discovered.



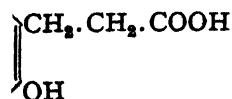
Coumarin can also be obtained by the action of sulphuric acid on a mixture of phenol and malic acid (*von Pechmann*), and substituted coumarins from sulphuric acid, phenols and esters of acetoacetic or monoalkyl-acetoacetic acids.

Coumarin is the lactone of *o*-hydroxycinnamic acid and is in fact an α -pyrone derivative (p. 704). It is generally classified as a heterocyclic compound. Its structure follows from hydrolysis and alkali fusion (see above) as well as from synthesis. Confirmation of the structure comes from two reactions. When coumarin is boiled with alkali and dimethyl sulphate, hydrolysis occurs with the formation of the sodium salt of coumarinic acid which is immediately methylated. Acidification gives

the stable *o*-methoxycinnamic acid, $\text{C}_6\text{H}_4 \begin{array}{l} \text{CH:CH.COOH} \\ \diagdown \\ \text{OCH}_3 \end{array}$ Another stable product is obtained if coumarin is first reduced to 3:4-dihydro-coumarin and then hydrolysed. Melilotic acid is thus obtained.



Dihydrocoumarin

H₂O

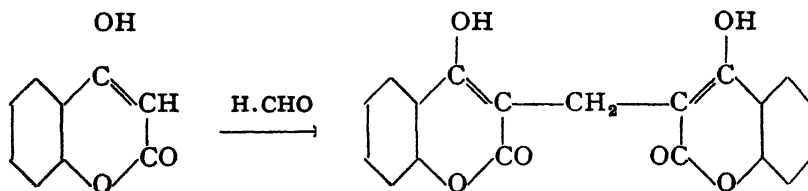
Melilotic acid

These two reactions are reliable tests for detecting coumarins.

Coumarin is used in the preparation of perfumes (essence of woodruff) and perfumed tobacco.

Dicoumarin, 3 : 3'-methylene-bis-4-hydroxycoumarin, is now used in medical practice as an anticoagulant. Until recently the substance used in the treatment of thrombosis (blood clotting) was *heparin*, a derivative of glucuronic acid and glucosamine. Heparin, however, has certain disadvantages ; it is effective only when given parenterally and its effect lasts only a short time.

For many years it has been known that cattle when fed on spoiled sweet clover develop hæmorrhage, and this effect was traced to the presence in the clover of some active principle. Link and his collaborators at the Wisconsin College of Agriculture have shown that this principle is dicoumarin, a substance which Anschutz synthesised in 1903 by the action of formaldehyde on 4-hydroxycoumarin.

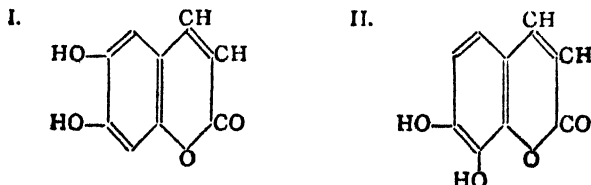


The clinical value of dicoumarin is enhanced by its lasting effect and the fact that it can be taken orally.

Umbelliferone, 7-hydroxy-coumarin, $\text{HO} \cdot \text{C}_6\text{H}_3 \begin{matrix} \text{CH:CH} \\ | \\ \text{O-CO} \end{matrix}$, is found in the bark of

Daphne mezereum, and is produced by the distillation of resins obtained from a number of the *umbellifera*. It may be synthesised by Perkin's reaction from β -resorcy-aldehyde acetic anhydride and sodium acetate, or in a similar manner to coumarin from resorcin and malic acid. It melts at 240° and is the lactone of *p*-hydroxy-*o*-coumaric acid or *umbellic acid*, $(\text{HO})_2\text{C}_6\text{H}_3 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$.

Among substitution derivatives of coumarin may be mentioned the structurally isomeric dihydroxy compounds *aesculetin* (I) and *daphnetin* (II).



The former is a disruption product of the glucoside *aesculin*, occurring in the horse chestnut, and the latter of the glucoside *daphnin*, found in members of the *Daphne* family. Aesculetin and daphnetin are prepared by Perkin's reaction, by heating hydroxy-hydroquinone-aldehyde and pyrogallaldehyde respectively with acetic anhydride and sodium acetate. They may be regarded as inner anhydrides (δ -lactones) of trihydroxycinnamic acids ; the latter are not stable in the free state, but only in the form of ether-acids or ether-esters.

Di- and Trihydroxy-Monocarboxylic Acids

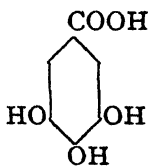
Dihydroxy-acids may be derived from the three dihydric phenols, pyrocatechol, resorcinol and hydroquinone. All the six possible isomerides are known.

Protocatechuic acid, $C_6H_3 \begin{cases} CO_2H[1] \\ OH[3] \\ OH[4] \end{cases}$, is formed from various

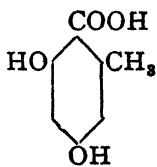
resins (catechu, gum benzoin, myrrh and particularly kino) by fusion with alkali. It may also be obtained from pyrocatechol by heating it to 140° with ammonium carbonate.

According to theory, there should be six possible trihydroxy-benzoic acids, three of which are known.

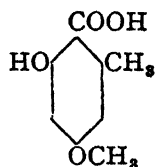
Gallic acid, 3:4:5-trihydroxy-benzoic acid, $C_6H_2(OH)_3COOH$, is found in tea, nut-galls, the fruit of *Cæsalpina coriaria* (*Divi-divi*), the root of the pomegranate and in many other plants. It is usually prepared from tannin by boiling with dilute acids, and may be synthesised from bromo-dihydroxy-benzoic acid or bromo-protocatechuic acid by fusion with potash. On heating to about 220° it undergoes decarboxylation to yield carbon dioxide and pyrogallol. Solutions of its alkali salts absorb oxygen from the air and become brown in colour. With ferric chloride it gives a blue-black precipitate.



Gallic acid



Orsellinic acid

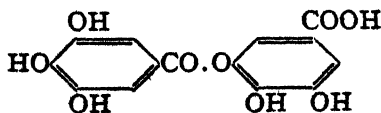


Everninic acid

Orsellinic acid is of importance in connection with the chemistry of lichens, from which source it may be extracted. It is prepared by oxidising the readily obtainable orcyl aldehyde, or from the methyl ester of dihydro-orsellinic acid. On partial methylation with diazomethane it yields everninic acid, $CH_3O(4).C_6H_2.OH(6).CH_3(2).COOH(1)$, which is also produced by boiling *evernic* and *ramalic acids* (present in many lichens) with baryta.

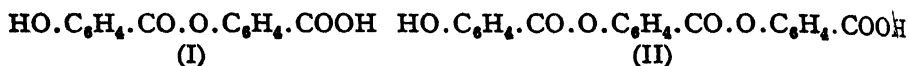
Depsides

m-Digallic acid occurs among the decomposition products of tannin and is a simple example of a class of substances which were intensively investigated by Emil Fischer and named by him *depsides* (from the

*m*-Digallic acid

Greek word meaning *to tan*). They are formed by the combination of two aromatic hydroxy-carboxylic acids, the carboxyl group of one condensing with the hydroxyl group of the other. The **depsides** are thus esters.

When two hydroxy-acids unite the product is a *di-depside*, and higher members of the series are *tri*-, *tetra-depsides* and so on according to the number of hydroxy-acid molecules linked together. *m*-Digallic acid is an example of a di-depside, an even simpler example being the depside of *p*-hydroxybenzoic acid (I), from which by the addition of another

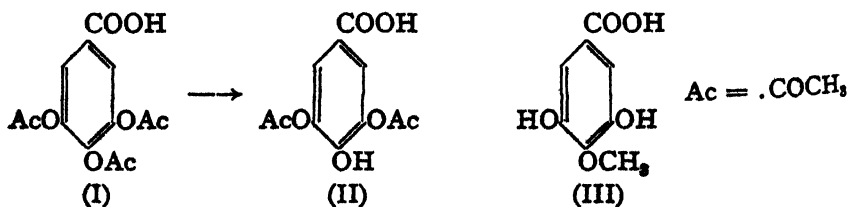


molecule of *p*-hydroxybenzoic acid is obtained the tridepside (II).

Emil Fischer carried out a systematic investigation of depside synthesis which proved to be more difficult than might at first sight be expected. It is well known that peptides are synthesised by amide-formation and it might be thought that the depsides would likewise be easily prepared by the allied process of esterification. It must be realised, however, that in peptide formation a basic (amino) group reacts with an acidic (carboxyl) group, whereas in depside formation linkage is effected between two acidic groups (carboxyl and phenolic) and consequently is not so straightforward. Other difficulties (including intramolecular rearrangement, see below) are also encountered. Fischer overcame these obstacles by "protecting" all but one of the reactive phenolic groups, and then condensing that group with the acid chloride of the appropriate acid. As a protecting group he used the carbomethoxy or the acetyl radical. The former is easily introduced by the combined action of methyl chloroformate and alkali on the phenolic acid in cold aqueous solution. *e.g.* *p*-hydroxybenzoic acid readily forms *carbomethoxy-p-hydroxybenzoic acid*.

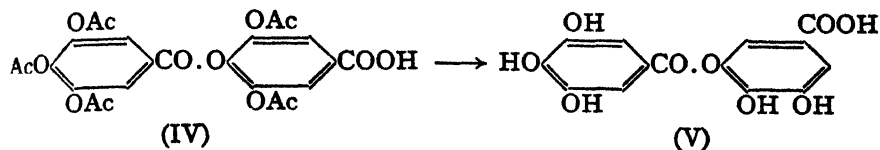


Acetylation of course presents little difficulty but to obtain selectively acetylated acids is not always so easy. An example is furnished by the acetylation of gallic acid which yields triacetylgallic acid (I), controlled hydrolysis of which gives 4-hydroxy-3:5-diacetoxygallic acid (II). The structure of this acid was established by methylation with diazo-

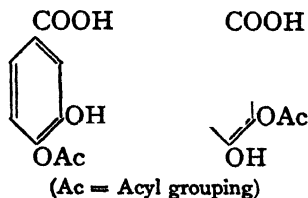


methane and subsequent hydrolysis to give 3:5-dihydroxy-4-methoxybenzoic acid (III).

Condensation of the acid (II) with fully acetylated galloyl chloride gives the pentaacetate of *p*-digallic acid (IV), but hydrolysis of this compound is accompanied by intramolecular change and the final product is not *p*- but *m*-digallic acid (V).



Many other instances of this change in which an acyl group migrates from a hydroxyl group *para* to a carboxyl group to a *m*-hydroxyl group have been encountered in this series. No explanation of this behaviour has been forthcoming.

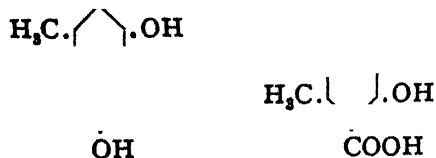


By these methods Fischer prepared numerous depsides including the didepsides *lecanoric acid* and *evernic acid*, which are present in lichens (see below).

Properties.—The depsides are esters and in consequence are decomposed by hydrolysis with dilute alkali into their components. The didepsides of gallic, protocathechuic, gentisic and β -resorcylic acids precipitate dilute solutions of glue, and give a precipitate with quinine acetate even at high dilutions. In this property they differ from the parent phenolic acids and resemble the tannins. The significance of the depsides in tannin chemistry is discussed later.

So far as is known, the lichens form the only natural source of depsides. Lichens are a result of the symbiosis (lit. *living together*) of algæ and fungi, and their peculiar morphological character goes hand in hand with their unusual chemical composition, as shown in their content of depsides. Among the latter the best known representative is lecanoric acid.

Lecanoric acid, *p-di-orsellinic acid*, is a di-depside of the formula



It may be isolated from various lichens, and has been synthesised by methods already described from orsellinic acid.

Evernic acid, monomethyl-lecanoric acid, contains a methoxyl in the *p*-position to the depside group (see previous formula), since the evernic acid obtained (together with orsellinic acid) from it on hydrolysis has the formula shown on p. 541. It can be synthesised from evernic and orsellinic acids by the same methods as were used for lecanoric acid.

THE TANNINS

Under the name tannin are included numerous vegetable products possessing the property of combining with animal hide to render it pliant and non-putrescible. The tannins have the following characteristics. They are amorphous and readily dissolve in water to give solutions with an astringent taste: they give intense green or blue colours with ferric chloride: and they precipitate proteins from aqueous solutions.

The chemical investigation of the tannins has proved to be difficult and arduous principally because they are amorphous and consequently are not readily purified or characterised. Our knowledge of their chemical constitution is still incomplete and is based largely on the work of Emil Fischer, K. Freudenberg, and M. Nierenstein.¹

The tannins are conveniently classified from the chemical standpoint by division into three groups which are differentiated by their behaviour towards dilute mineral acids.

(1) Those tannins which are related to the depsides and are hydrolysed with dilute mineral acid mainly to gallic acid and glucose. To this class belong Chinese tannin, Turkish tannin, and hamameli-tannin.

(2) Those tannins which are related to diphenyldimethylolids and on hydrolysis yield mainly ellagic acid and glucose.

(3) The **phlobatannins** which with dilute hydrochloric acid yield **phlobaphenes**—dark coloured amorphous insoluble substances: and the tannins related to catechin.

Depside Tannins

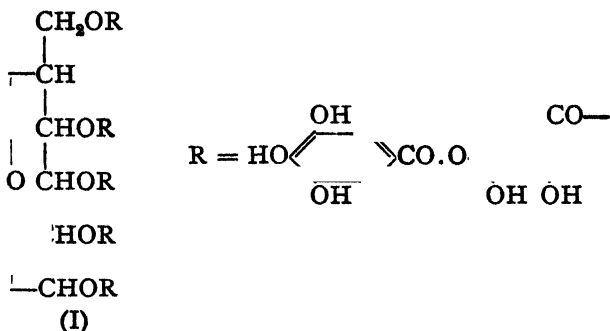
The typical and most important tannin is **tannic acid** which is present in large amount (*ca.* 50 per cent.) in gall-nuts, which are pathological growths in the leaves and twigs of certain species of oak caused by the puncturing of the tissues by the gall wasp. It is usually termed **gallo-tannic acid** to distinguish it from other varieties of tannic acid.

Gallotannic acid is prepared from finely divided gall-nuts by extraction with a mixture of ether and alcohol, and when pure is a colourless amorphous substance, which dissolves readily in water and sparingly in alcohol and ether. The aqueous solution possesses a bitter astringent taste and is coloured dark blue by ferric salts, hence its use in the

¹ "The Natural Tannins," by A. Russell, *Chem. Reviews*, 1935, 17, 155. "Natural Organic Tannins," by M. Nierenstein (London, 1934).

manufacture of ink.¹ Tannic acid is withdrawn from its aqueous solution by animal hide, the latter being "tanned" and converted into leather. Tannin also precipitates many alkaloids and proteins from their solutions. This reaction provides one of the most sensitive tests for proteins. The use of tannic acid as a mordant for basic dyestuffs was introduced by W. H. Perkin. It is also employed in medicine and for the clarification of wine.

Gallotannic acid has a high molecular weight and on hydrolysis with dilute sulphuric acid yields gallic acid and glucose in the ratio of 10 : 1. An important clue to the structure of the acid was obtained by Emil Fischer who introduced five *m*-digallic acid groups into D-glucose and obtained a penta-*m*-digalloyl- β -glucose (I) which showed a strong resemblance to the gallotannic acid from Chinese galls.



Efforts to confirm this picture by isolating *m*-digallic acid from the hydrolytic products of tannin have been unsuccessful. The most that has been accomplished has been to isolate trimethylgallic acid and 3 : 4-dimethylgallic acid from the products of hydrolysis of methylated tannin.

1-Galloyl- β -glucose has been identified with the glucogallin of Chinese rhubarb.

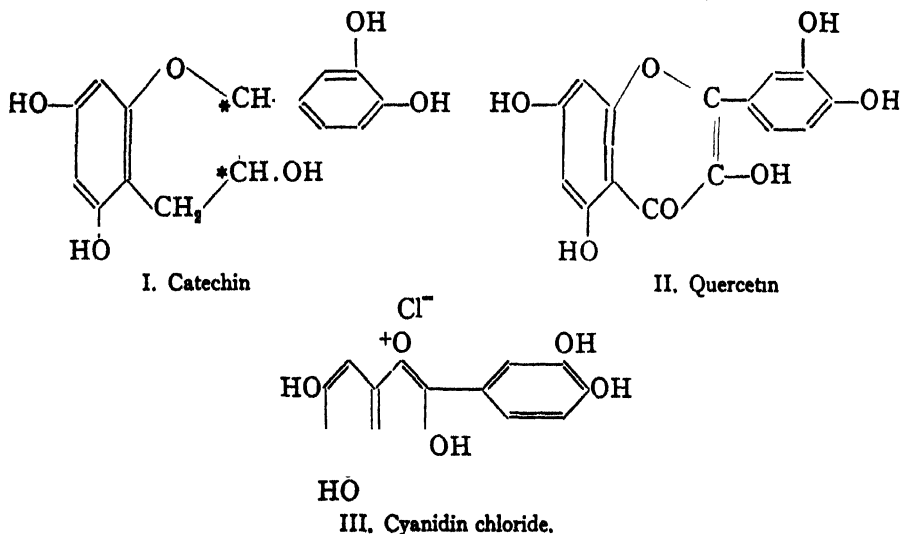
Catechins.—This group includes a number of isomeric compounds of the composition $\text{C}_{15}\text{H}_{14}\text{O}_8$ which are present in *cutch* or *catechu*, a product prepared from various plants by extraction with hot water. *Gambier catechu* is obtained from the bush *Uncaria gambier* (Malacca, Penang, Singapore); *Bengal* or *acacia catechu* from the wood of *Acacia catechu* (India, Burma); *Bombay* or *areca catechu* from the fruit of the betel nut palm tree, *Areca catechu* (Asia); and *mangrove cutch* from

¹ Ordinary writing inks commonly consist of a solution containing tannic acid (or aqueous extract of gall-nuts) and ferrous sulphate, together with certain acidic substances, gum, and phenol (to prevent mouldiness). The ferrous salt of tannic acid is first formed, or the tannic acid may become hydrolysed, giving the salt of gallic acid. These salts are soluble and only feebly coloured, and the small amount of acid (HCl or H_2SO_4) present prevents the untimely precipitation of black ferric compounds. When used for writing the acidity of the ink is neutralised by the alumina present in the paper. Oxidation then occurs and a black insoluble iron precipitate, stable to light, is formed. Owing to the pale colour of the unoxidised ink it is usual to add dyes, such as soluble indigo or aniline blue, to the above mixtures.

the bark of the mangrove, *Ceriops candolleana*. The pure catechins are colourless crystalline derivatives of phloroglucinol. They form the basis of many natural tannins, and under the influence of mineral acids, enzymes or heat they readily change into amorphous tannins or tannin reds.

The constitution of these compounds proved to be an exceedingly difficult problem, but the researches of Freudenberg, based on earlier work of Kostanecki and of A. G. Perkin, have shown the catechins to be isomerides of the following structure I. This constitution is closely related to that of the flavone dye-stuffs ¹ (e.g. quercetin II) and the anthocyanidins (e.g. cyanidin chloride III). The relationship to the natural flower pigments was proved ² by the conversion of cyanidin chloride into *r*-epicatechin by reduction in alcoholic solution, using platinum black and hydrogen.

As may be seen from formula I, these compounds may exhibit *cis* and *trans* isomerism due to a different arrangement of the groups around the two C-atoms marked *.



In addition the two marked atoms are asymmetric, thus giving rise to optically active and racemic forms of catechin and *ep*icatechin.

Cutch or catechu is also used as a dye, giving a fast brown colour on cotton. For this purpose it is employed in combination with copper sulphate followed by treatment with potassium bichromate. It is also used as a preservative for fishing nets, sailcloth, etc.

¹ Formula I for catechin and the relationship to quercetin were first suggested by A. G. Perkin and Yoshitake, *J.*, 1902, 81, 1162; 1905, 87, 398. ² Freudenberg and co-workers, *Ann.*, 1925, 444, 134.

XIII

Compounds containing Benzene Nuclei
united by Carbon Linkings

Many of the methods described in the foregoing sections for introducing alkyl groups into the benzene nucleus may also be employed for the introduction of phenyl, benzyl and other aromatic groups. In this way compounds are formed containing benzene nuclei linked together directly, or through the medium of one or more carbon atoms. The simplest examples of this kind are in the diphenyl group.

I.—DIPHENYL GROUP

Diphenyl, $C_6H_5 \cdot C_6H_5$, the parent hydrocarbon of this series is best prepared by *Ullmann's* method, in which iodobenzene is heated to 220° with finely-divided copper.



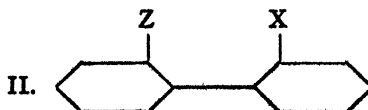
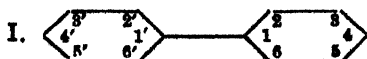
This process recalls Fittig's synthesis, but is of far greater general utility. It can be applied successfully to a variety of iodo and bromo substitution products of benzene, with the production of symmetrical diphenyl derivatives. The reaction between copper and the iodo-compound proceeds at 210° to 220° , and the constitution of the synthetic product can be deduced directly from that of its components. Bromo compounds, especially those in which the halogen atom is activated by an electronegative group in the ortho or para position, also react readily.

Diphenyl is prepared industrially by the pyrogenetic decomposition of benzene, and furnishes an example of nuclear dehydrogenation of an aromatic compound.



Diphenyl is also found in coal tar. It forms colourless crystals which melt at 70° , boil at 254° , and are readily soluble in alcohol and ether. With ozone it yields a *tetra-ozonide*. It is widely used in fluid heat transmission systems.

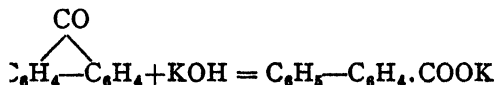
The position of substituents in the diphenyl molecule is usually indicated by numbers as in formula I. With two or more substituents it will be seen that there are numerous possibilities of isomerism. In addition, isomerism of another type may occur when two or more of the ortho-positions to the common bond joining the benzene nuclei are substituted as in II (X and Z may also be identical). This isomerism is discussed fully on p. 38.



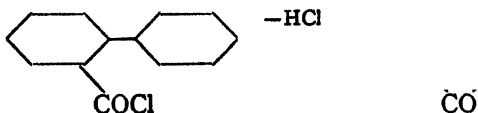
Benzidine, 4:4'-*diamino-diphenyl*, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_4 \cdot \text{NH}_2$, is obtained as described on p. 477 by intramolecular rearrangement of hydrazobenzene. In its technical preparation nitrobenzene is reduced with zinc dust and sodium hydroxide, and the hydrazobenzene so formed is converted into benzidine by heating with acid. The compound may either be isolated as the free base by addition of sodium hydroxide, or as the sparingly soluble sulphate. Benzidine crystallises from hot water in leaflets, m.p. 122° , and is largely used in the manufacture of substantive azo-dyes (see p. 491 *et seq.*). The *sulphonic acids* obtained by the action of concentrated sulphuric acid on benzidine are employed for the same purpose.

Tolidine, 3:3'-*dimethyl-4:4'-diaminodiphenyl*, m.p. 128° , is a homologue of benzidine and is prepared in a similar manner from *o*-nitrotoluene; *o*-dianisidine, 3:3'-*dimethoxy-4:4'-diaminodiphenyl*, is obtained from *o*-nitroanisole.

Diphenyl-2-carboxylic acid, m.p. 111° , is obtained by fusing *fluorenone* (p. 552) with potassium hydroxide.



On treatment with strong sulphuric acid fluorenone is regenerated by removal of the elements of water. A similar ring closure is undergone by the acid chloride on distillation.



Diphenic acid, *diphenyl-2:2'-dicarboxylic acid*, m.p. 229° , is obtained by oxidising phenanthraquinone with a mixture of potassium bichromate and sulphuric acid. This reaction has given valuable information as to the constitution of phenanthrene (p. 610).

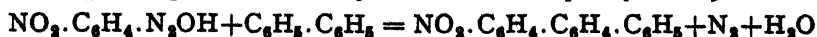
Another method of preparing diphenic acid is by the action of an ammoniacal solution of cuprous oxide on diazotised anthranilic acid.¹ When heated with soda lime it yields diphenyl, and on strong oxidation is converted into phthalic acid. The structure of the acid follows from these reactions.

A number of hydrocarbons built up of a series of benzene rings linked together in the *p*-positions have recently been prepared. **Terphenyl**, *p-diphenyl-benzene*, m.p. 210° , was obtained by the interaction of azobenzene, benzene, hydrogen chloride and aluminium chloride. An intermediate product in the process is *amino-terphenyl*, which was deaminated in the usual way (p. 480).

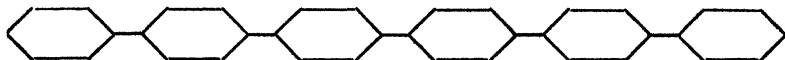


¹ E. H. Huntress, *Organic Syntheses*, vii, 30.

The corresponding nitro-terphenyl has also been prepared by the interaction of *p*-nitrophenyl diazo hydroxide with diphenyl.¹ By converting



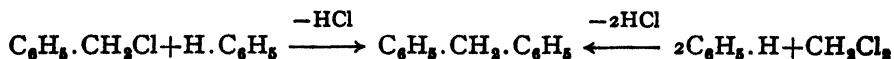
amino-terphenyl into the iodo-compound and heating the latter with silver powder at 330° (*Ullmann's* method) **sexiphenyl**, m.p. 475°, has been prepared.² These are colourless hydrocarbons which sublime well below their melting-points.



II.—DIPHENYLMETHANE AND FLUORENE GROUPS

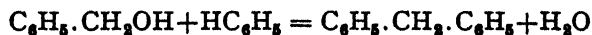
Diphenylmethane, $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$, forms needles, m.p. 26° and b.p. 262°, and has an odour of oranges. It may be obtained by the following methods:—

1. By the action of benzyl chloride, or of methylene chloride, on benzene in the presence of aluminium chloride.

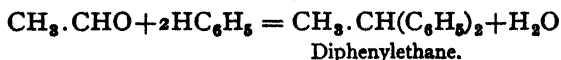


Various substitution products of benzene may also be employed (*e.g.* homologues, phenols, tertiary amines), leading to the formation of ring-substituted diphenylmethanes.

2. By the condensation of benzyl alcohol with benzene under the influence of concentrated sulphuric acid.



Homologues of diphenylmethane containing substituents in the methylene group are obtained in a similar manner by condensing aliphatic aldehydes or ketones with benzene, *e.g.*,



This last reaction permits the preparation of a number of diphenylmethane derivatives, since, on the one hand, we may use different aldehydes and ketones and, on the other, numerous substitution products of benzene.

Benzophenone, $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{C}_6\text{H}_5$, the ketone corresponding to diphenylmethane, is formed when the latter is oxidised with chromic acid. This compound and the secondary alcohol *benshydrol*, $\text{C}_6\text{H}_5 \cdot \text{CHOH} \cdot \text{C}_6\text{H}_5$, have been described on p. 525.

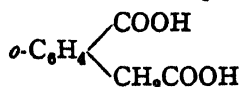
Indene and Fluorene

A compound closely related to diphenyl and diphenylmethane is **fluorene**. To understand the chemical behaviour of this hydrocarbon, however, it is first necessary to discuss briefly another coal tar hydrocarbon, **indene**.

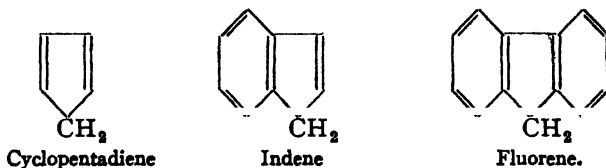
¹ H. France, I. M. Heflbron and D. H. Hey, *J.*, 1938, 1364.
Ber., 1924, 57, 84.

² Pummerer and Bittner,

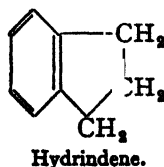
Indene.—As will be seen from the formula, indene contains a benzene nucleus condensed with a cyclo-pentadiene ring. It is present in coal tar, and may be isolated from the "heavy oil" by fractionation and subsequent precipitation with picric acid. A simpler method is to heat the crude indene with sodium at 140° to 150° , when sodium indene is formed as a glassy mass. This on treatment with water yields very pure indene, C_9H_8 . It is a colourless oil, b.p. 178° . The structure of indene follows from its oxidation to homophthalic acid,



Methylene groups that lie between two double bonds are extremely reactive, and the methylene groups in cyclopentadiene, indene and fluorene are no exceptions (see pp. 390 and 552). For example, they all form



sodium compounds and condense with aldehydes in presence of alkali to form benzylidene compounds. These methylene groups, therefore, closely resemble those activated by unsaturated groups—nitro, carbonyl, etc.—in compounds such as nitromethane and acetone.



Indene readily takes up oxygen from the air and has a strong tendency to polymerise. With nitric acid it is oxidised to phthalic acid, and on reduction with sodium and alcohol, or more simply by catalytic hydrogenation, it is converted into *hydrindene*, C_9H_{10} .

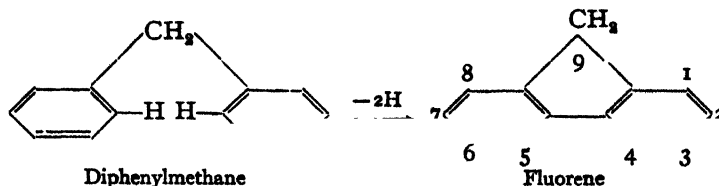
The unsubstituted aromatic hydrocarbons which are discussed in this book contain an even number of carbon atoms; *e.g.* benzene (6), naphthalene (10), etc. Indeed an even number of carbon atoms is essential if a hydrocarbon is to possess purely aromatic character. There are, however, many hydrocarbons included in the aromatic series which have an odd number of carbon atoms. These hydrocarbons as we shall see, behave not only as aromatic substances, but exhibit other characteristic properties. Indene is such a compound. In the sequel we shall consider another hydrocarbon of this type, fluorene, which contains two benzene rings fused to the five-membered cyclopentadiene nucleus.

Fluorene¹

Fluorene is closely related structurally to diphenyl and diphenylmethane. This relationship to diphenylmethane is shown both by the

¹ See G. Rieveschl and R. F. Ray, *Chem. Rev.*, 1938, 23, 287.

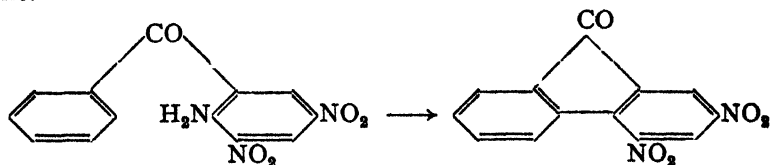
passage of diphenylmethane into fluorene by pyrolytic dehydrogenation and by the similarity of the ultra-violet absorption spectra of the two hydrocarbons.



Fluorene is present in coal tar to the extent of about 1.6 per cent. and is isolated through its sodium or potassium derivative from which the hydrocarbon is formed by treatment with water. It melts at $114^{\circ}\text{C}.$, boils at $298^{\circ}\text{C}.$, and crystallises in beautiful white flakes. Fluorene generally has a strong violet fluorescence (hence its name), but when absolutely pure shows no fluorescence.

Substituted fluorenes can be obtained from fluorene by nitration, bromination, etc., but most substituted fluorenes have to be synthesised, and a number of methods are available for this purpose though the yields are often unsatisfactory.

(1) *Ullmann method*.¹—This method is based on the conversion of *o*-aminobenzophenone into fluorenone (in which the CH_2 group of fluorene is replaced by $\text{C}=\text{O}$) by diazotisation followed by removal of the diazo group. 2-Amino-3:5-dinitrobenzophenone thus yields 2:4-dinitrofluorenone. Reduction of the carbonyl group then affords the fluorene.



(2) Another process starts from phenanthraquinone and its derivatives. When boiled with aqueous alkali, phenanthraquinone yields 9-hydroxyfluorene-9-carboxylic acid. Substituted phenanthraquinones undergo a

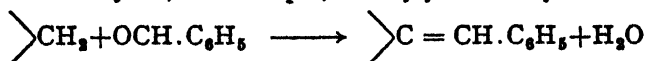


similar reaction to give the corresponding acids. These acids can then be transformed into other derivatives of fluorene. Most of these acids, when heated with acetic anhydride in the absence of air, lose carbon dioxide to form the acetyl derivative of the corresponding fluorene-9-ol (9-hydroxyfluorene); when boiled with acetic anhydride, water, or alkalis in the presence of air, oxidation occurs simultaneously with the production of a substituted fluorenone.

¹ Ullmann and Mallet, *Ber.*, 1898, 31, 1694. A useful modification of the method is that of W. C. Lothrop and P. A. Goodwin, *J.A.C.S.*, 1943, 65, 363.

The structure of fluorene follows from its oxidation to fluorenone which as already stated (p. 548) is converted by alkali fusion into diphenyl-2-carboxylic acid. This acid on decarboxylation yields diphenyl and on ring-closure regenerates the parent compound, fluorenone.

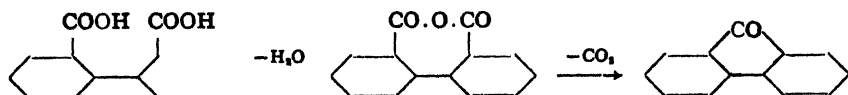
Fluorene may be regarded as a cyclopentadiene derivative and the reactivity of the methylene group towards sodium or potassium, aromatic aldehydes, nitrosobenzene, and oxidation is therefore not surprising. The aromatic aldehydes, for example, readily yield benzylidene derivatives :



In many ways, however, fluorene behaves as a diphenyl derivative, the presence of the five-membered ring altering the properties of the diphenyl nucleus only to a slight extent. Nitration yields 2-nitrofluorene: this on further nitration gives chiefly 2:7-dinitrofluorene (66 per cent.), but some of the 2:5-isomer (22 per cent.) is also obtained. The trisubstituted derivatives have not been intensively investigated. The structures of substituted fluorenes so obtained are determined by converting them into the corresponding diphenyl-2-carboxylic acids.

Fluorene is a resonance hybrid¹ with contributing forms represented by structures such as the one given on p. 550.

Fluorenones.—Fluorenone is best prepared from fluorene by oxidation with sodium dichromate and glacial acetic acid.² It is also prepared by heating diphenic acid at 360° and this method is frequently used to prepare substituted fluorenones.



Fluorenone is a yellow crystalline compound, m.p. 84°, which is best purified by distillation. It gives the reactions characteristic of aromatic ketones. Reduction with zinc dust gives the secondary alcohol *fluorenol*, which is reduced by red phosphorus, iodine, and water to fluorene. Clemmensen reduction of fluorenone likewise gives fluorene, but the two-stage process is preferable. The five-membered ring may be broken by the action of alkali in diphenyl ether at 180° C.,³ substituted diphenyl-2-carboxylic acids being formed. 2-Chlorofluorenone thus gives 4'-chlorodiphenyl-2-carboxylic acid. The method is of great service in determining the constitution of substituted fluorenones.



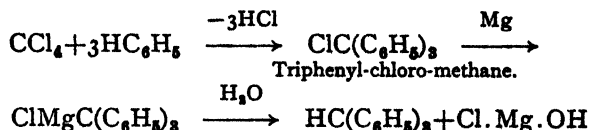
¹ W. C. Lothrop, *J.A.C.S.*, 1939, 61, 2115. ² E. H. Huntress, E. B. Hershberg and I. S. Cliff, *ibid.*, 1931, 53, 2720; 1933, 55, 2559. ³ E. H. Huntress and M. K. Seikel, *ibid.*, 1939, 61, 816.

III.—TRIPHENYLMETHANE GROUP

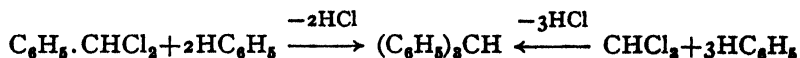
This group is of practical as well as theoretical importance. On the one hand it includes a series of widely-used dye-stuffs—the rosanilines, aurines and phthaleins—and on the other it contains compounds which have aroused very great interest in recent years owing to their unexpected properties.

Triphenylmethane, $(C_6H_5)_3CH$, m.p. 92° , b.p. 358° , the parent substance of the whole group, is obtained by the following reactions.

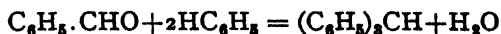
1. From the magnesium compound of triphenyl-chloro-methane by decomposition with water and acid. This is the most convenient method of preparing the hydrocarbon, since triphenyl-chloro-methane is easily obtained by treating carbon tetrachloride with benzene and aluminium chloride.



2. By the action of aluminium chloride on a mixture of benzal chloride and benzene, or of chloroform and benzene.



3. From benzaldehyde and benzene, or benzhydrol and benzene, under the influence of dehydrating agents such as zinc chloride.

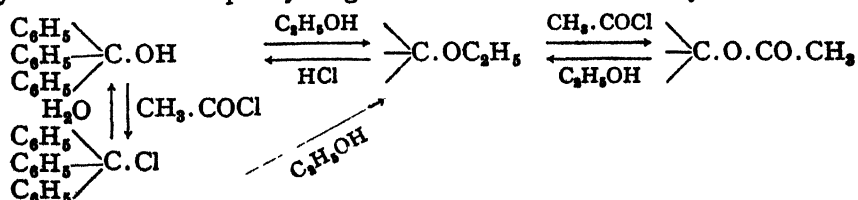


By means of these reactions substituted derivatives of triphenylmethane may also be prepared. If, for example, in method 3, dimethylaniline is used in place of benzene, the leuco-base of malachite green is formed. This important compound is described later.

Triphenylmethane is a white, crystalline substance, which is insoluble in water and cold alcohol, but readily dissolves in hot alcohol, ether and benzene.

Potassium triphenylmethane, $(C_6H_5)_3CK$, is obtained by heating the hydrocarbon with potassium.

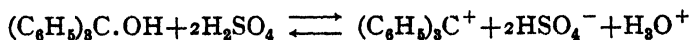
Triphenyl-carbinol, $(C_6H_5)_3C.OH$, m.p. 163° , is readily prepared by the action of phenylmagnesium bromide on methyl benzoate or



benzophenone. The carbinol possesses interesting properties, possessing as it does a very reactive hydroxyl group and an aptitude for forming

carbonium ions. Triphenylcarbinol extremely readily forms alkyl ethers with alcohols in the presence of hydrogen chloride. The ethyl ether is unusually reactive. It is easily hydrolysed to the carbinol with dilute mineral acids, and when treated with acetic anhydride or acetyl chloride yields the acetyl derivative of triphenyl-carbinol. Crystallisation of the acetyl derivative from ethanol gives a quantitative yield of the ethyl ether. It is also noteworthy that triphenylmethylcarbinol is not acetylated by acetyl chloride, but instead gives triphenylmethyl chloride (triphenyl-chloromethane). This in fact is a very good method for preparing the chloro-compound in the laboratory.

Triphenylcarbinol is a weak base. When treated in ethereal or benzene solution with hydrogen chloride it is quantitatively converted into triphenylchloromethane. The carbinol dissolves in concentrated sulphuric acid to give a yellow solution, which shows a molar freezing-point depression four times that of a non-electrolyte. This depression is the result of the carbinol reacting with the acid to form a *carbonium ion* according to the equation :



Carbonium ions occur as reactive intermediates in many reactions effected by mineral acids, aluminium chloride, etc. (see *e.g.* p. 407).

Triphenylmethyl chloride, $(\text{C}_6\text{H}_5)_3\text{CCl}$, m.p. 111° , is prepared as already described. It is manufactured from carbon tetrachloride and benzene (p. 553). The chlorine atom in the compound is very mobile and easily detached. With water, for example, hydrolysis occurs slowly in the cold and immediately on boiling, to form triphenylcarbinol and hydrochloric acid. With ethanol it reacts readily to give the ethyl ether of triphenylcarbinol, m.p. 78° .

Triphenylmethane Dye-stuffs

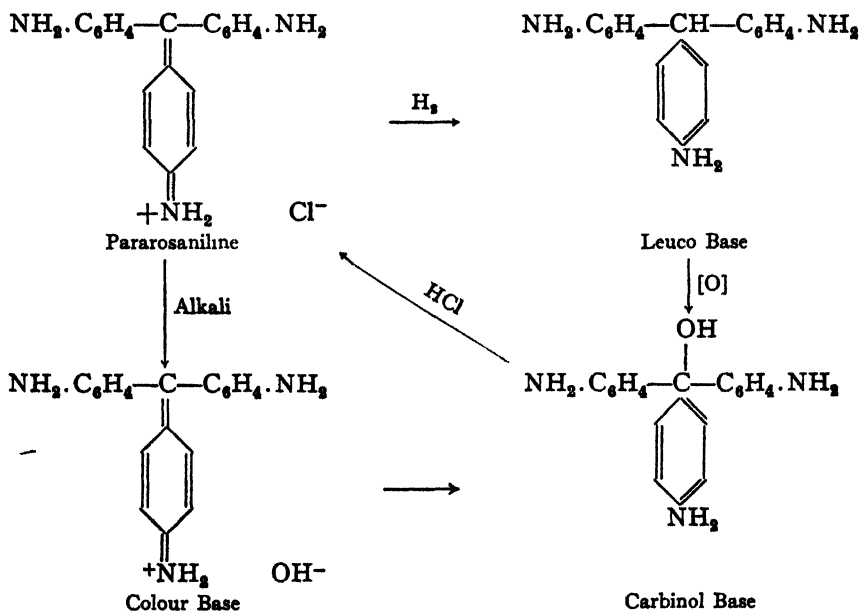
From the colourless hydrocarbon, triphenylmethane, the leuco-compounds of dye-stuffs may be derived by replacing hydrogen in the benzene nuclei by certain groups of atoms. Chief among the latter are the amino-group, in which hydrogen may also be substituted by alkyl radicals, and the hydroxyl group. For the function of these auxochromes see p. 80. In addition to the derivatives discussed on p. 534, in connection with phthalic anhydride, we have the three following series :

1. The Malachite Green group, derived from diaminotriphenylmethane.
2. The Rosaniline group, derived from triaminotriphenylmethane.
3. The Aurine group, derived from trihydroxytriphenylmethane.

Constitution of the Triphenylmethane Dyestuffs

The relationship of these substances to triphenylmethane, which is discussed below, was first shown in 1878 by E. and O. Fischer. A subsequent development of importance was the introduction of the quinonoid formula by Nietzki, but opinions as to the finer structural details are almost as numerous as the researches on the di- and tri-phenylmethane dyestuffs themselves.

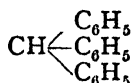
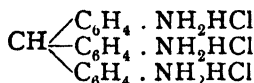
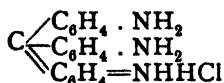
To illustrate the chemical changes which occur when the colourless substituted triphenylmethanes are converted into dyestuffs we shall consider the dye **pararosaniline** (the formula is given below). Triphenylcarbinol with one *p*-amino-group is colourless, but with concentrated hydrochloric acid a most striking change occurs and an orange-red dyestuff results. If a second *p*-amino group is introduced and the compound is acidified *Doebner's Violet* is produced. If, however, a third *p*-amino group is introduced the dyestuff pararosaniline is obtained, which in contrast to the first two dyestuffs is of great commercial importance. This change of the colourless carbinol base into a deeply coloured substance must be accompanied by some profound structural change, and there is little doubt that this is essentially the change of a benzenoid into a quinonoid form (see formulæ). Reduction of the dyestuff



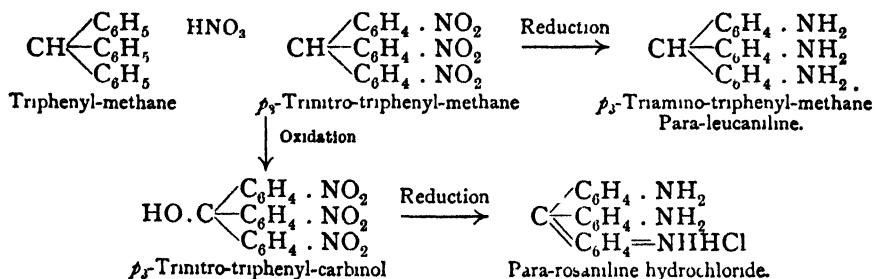
yields a colourless compound known as a **leuco-base** or **leuco-compound**, oxidation of which by means of lead peroxide in the presence of hydrochloric acid regenerates the dyestuff. It may be noted in passing that the use of these terms is not limited to the triphenylmethane series, but is common to the indigo dyestuffs, etc. If the oxidation of the leuco

base by lead peroxide is effected in the absence of acid the carbinol base is formed. The carbinol base is also obtained from the dyestuff by treatment with potassium hydroxide, an unstable colour base being first formed which immediately isomerises to the pseudo-base or carbinol base.

That pararosaniline is a triphenylmethane was shown in the following manner by E. and O. Fischer. Pararosaniline hydrochloride was reduced to the hydrochloride of paraleucaniline, and the latter converted by way of the diazonium salt into triphenylmethane :

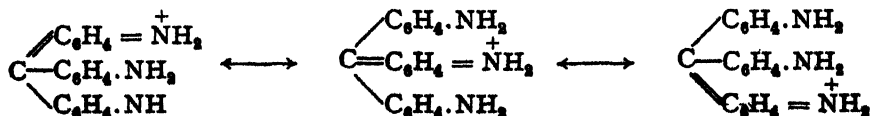


In addition, triphenylmethane was synthesised from benzene and chloroform in the presence of aluminium chloride, and converted by nitration into *p*₃-trinitro-triphenylmethane, from which para-leucaniline and para-rozaniline were obtained as follows :—



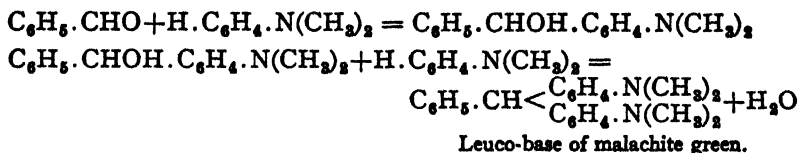
The orientation of the amino groups was determined in the following manner. Two molecules of aniline condense with one of benzaldehyde to give a diaminotriphenylmethane, tetrazotisation of which gives the corresponding dihydroxytriphenylmethane. Fusion of this compound with potassium hydroxide yields 4:4'-dihydroxybenzophenone, from which it follows that the two amino-groups in the diaminotriphenylmethane occupy *para*-positions. If now aniline is condensed with *p*-nitrobenzaldehyde and the nitro group reduced to the amino in the presence of hydrochloric acid, pararosaniline is obtained. The three amino groups in the dyestuff must therefore not only be in separate benzene rings, but must also be situated *para* to the methane carbon atom.

The triphenylmethane dyestuffs are resonance hybrids, the principal resonating structures of the pararosaniline cation being :



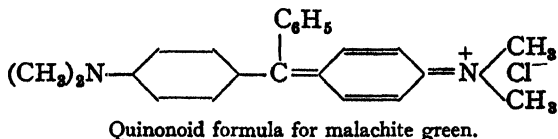
1. Malachite Green Dyestuffs

Malachite green, *Victoria green*.—When benzaldehyde is heated at 100° C. with pure dimethylaniline in the presence of condensing agents such as hydrochloric acid, sulphuric acid or zinc chloride, there is formed tetramethyl-di-*p*-amino-triphenylmethane or *leuco-malachite green*. Tomioka showed that in this reaction *p*-dimethylaminobenzhydrol is first formed: it then condenses with another molecule of dimethylaniline. In both stages hydrogen atoms in the *para*-position to the $N(CH_3)_2$ groups take part.



The leuco-base is obtained in colourless leaflets or prisms.

When the hydrochloride of the leuco-base is oxidised with lead peroxide the carbinol base is formed, which in the presence of acid loses one molecule of water to form the dye.



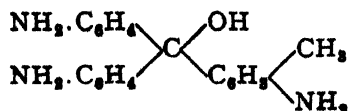
The compound is most conveniently isolated from solution in the form of the zinc double salt, $3(C_{23}H_{25}N_2Cl)$, $2ZnCl_2$, H_2O , by precipitation with zinc chloride and common salt, or the carbinol base may be precipitated with sodium carbonate, and converted into the oxalate, $2C_{23}H_{25}N_2$, $3C_2H_2O_4$, by treatment with oxalic acid.

The zinc double salt or the oxalate is placed on the market in the form of green crystals having a metallic sheen. Malachite green dyes wool, silk, jute, leather and tanned cotton a green colour, which is not very fast to light.

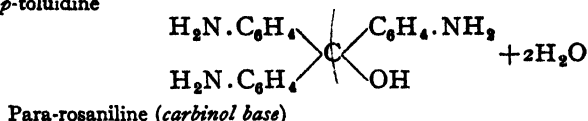
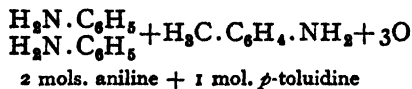
Brilliant green, *Guignet's green*, is the ethyl compound corresponding to malachite green, obtained by condensing diethylaniline with benzaldehyde.

2. Rosaniline Dyestuffs

The rosaniline dyestuffs are derived from triaminotriphenylcarbinol as already noted on p. 555, and from triaminodiphenyl-*m*-tolyl-carbinol (annexed formula). The conversion of the carbinol bases into the dyestuffs has already been discussed.

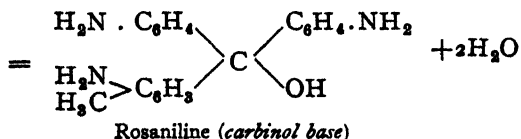
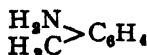


Para-rosaniline (*parafuchsine*) (constitution, see p. 555), is prepared by oxidising a mixture of *p*-toluidine (1 mol.) and aniline (2 mols.) with nitrobenzene in the presence of iron. It is supposed that the methyl group of *p*-toluidine is first oxidised to the aldehyde stage, and the *p*-amino-benzaldehyde so formed condenses with aniline as in the malachite green preparation (p. 558). Hence the "methane carbon atom" of para-rosaniline has its origin in the methyl group of *p*-toluidine.

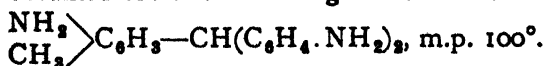


The colourless carbinol base—which is triacidic and more strongly basic than ammonia—unites with one equivalent of an acid with loss of water to form red dyes. Hydrochloric acid yields para-rosaniline hydrochloride or **para-fuchsine**, which is a constituent of technical fuchsine.

Rosaniline (*fuchsine*), is a homologue of para-rosaniline and is obtained by the above condensation when 1 mol. aniline is replaced by 1 mol. *o*-toluidine, *i.e.*, when an equimolecular mixture of aniline, *o*-toluidine and *p*-toluidine is oxidised. The additional methyl group is therefore situated in the *o*-position to an amino group.



Rosaniline in the solid state consists of green crystals with a metallic lustre. It dissolves in water, giving a deep reddish-purple colour. The solution dyes silk and wool directly, and cotton after having been mordanted with tannin and potassium hydrogen tartrate. But the red colours so obtained are not fast to light. On reduction, rosaniline gives *leucaniline*,



Magenta is one of the oldest of the synthetic dyestuffs and was obtained by Verguin in 1859 by the oxidation of impure aniline by tin chloride. Subsequent investigators used other oxidising agents, and A. W. Hofmann showed that pure aniline does not give the dye-stuff on oxidation. In practice an equimolecular mixture of aniline, *o*- and *p*-toluidine is oxidised.

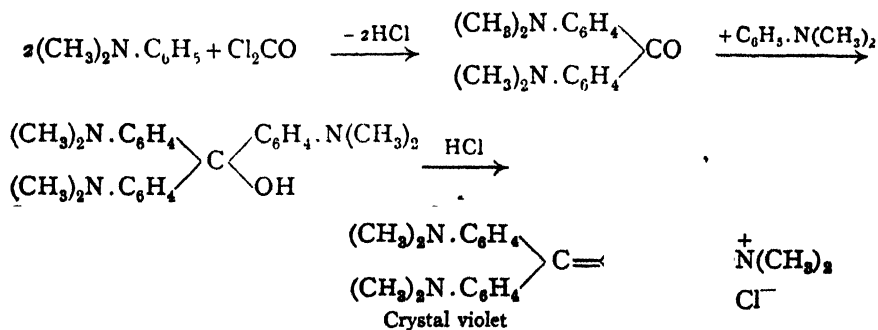
The Magenta so obtained is a mixture of rosaniline and para-rosaniline* with the former predominating.

Acid Fuchsine, acid magenta, $C_{20}H_{17}N_3(SO_3.ONa)_2$, is a disulphonic derivative of fuchsine, prepared by heating rosaniline with fuming sulphuric acid at 120° . It dyes wool and silk in weak acid bath, thus enabling fuchsine to be used as an acid dye.

Methylated Derivatives

When the hydrogen atoms of the NH_2 -groups in rosaniline and para-rosaniline are replaced by methyl or ethyl groups, the red colour of the dye is changed to violet. The tendency towards blue becomes more pronounced as the number of alkyl groups increases. Dimethyl-aniline (prepared by heating aniline with methyl alcohol and hydrochloric or sulphuric acid at 200°) has been used as starting material and oxidised directly to alkylated para-rosanilines, usually by means of cupric salts. In this manner **methyl violet** is obtained, consisting of a variable mixture of the hydrochlorides of tetra-, penta- and hexamethyl para-rosanilines. It is an iridescent green resinous mass, which dissolves in water to give a beautiful violet solution. If hydrogen is substituted by benzyl groups ($C_6H_5.CH_2-$), instead of methyl groups, a bluer shade is obtained (*benzyl violet*).

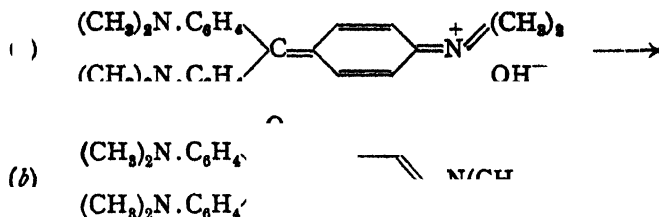
Crystal violet is the hydrochloride of pure hexamethyl para-rosaniline. It is prepared by the interaction of phosgene and dimethyl-aniline to form tetramethyl-diamino-benzophenone (Michler's ketone, p. 525), and condensing the latter with dimethyl-aniline in the presence of phosphorus chloride or aluminium chloride. It crystallises exceedingly well.



Constitution of the Rosaniline Colour Bases

When crystal violet (the hydrochloride of hexamethyl-triamino-triphenylmethane) is treated in solution with one equivalent of alkali, the coloured solution first obtained is strongly alkaline and conducts the electric current. In time, however, it becomes colourless, and finally the alkalinity vanishes and the conductivity falls. It appears therefore that,

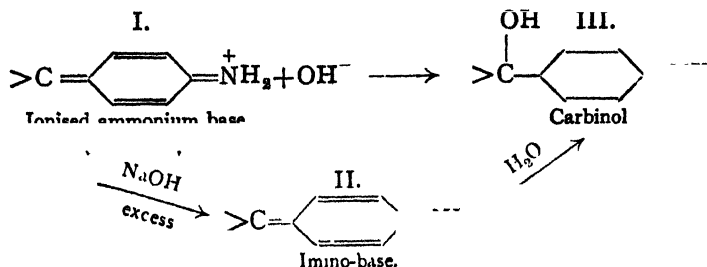
immediately after the addition of an equivalent of alkali to crystal violet the actual base of structure (a) is present in solution, and that this slowly isomerises to the carbinol base (pseudo-base) of formula (b).



Similar results are obtained with other bases of triphenylmethane dyestuffs, and the conclusions arrived at are summarised as follows:

The colour bases of the dye-salts of this series are ammonium hydroxide derivatives of the same colour as the salts. They cannot be isolated in the solid state but exist only in dilute aqueous solution, *i.e.*, in the almost completely ionised condition¹ (formula I).

Even in the dissociated state these dye-bases slowly undergo molecular rearrangement with variable but always measurable velocity to form the pseudo-bases or carbinol base (formula III). When the salt of a dye-base such as fuchsine, which still contains hydrogen attached to nitrogen, is treated in aqueous solution with *excess* of sodium hydroxide, an anhydrous base of different colour is precipitated (formula II). This can be extracted with indifferent solvents. Para-rosaniline, for example, yields a brown compound known as *Homolka's base*. These anhydrides are related to



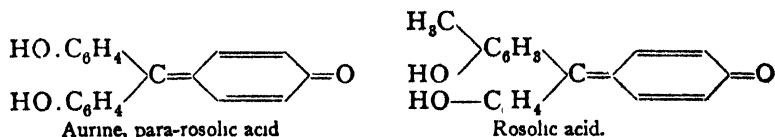
the primary dye-bases as ammonia is to ammonium hydrate. The imino-base is therefore not to be considered as the actual base of fuchsine, but rather as its anhydride. With acids it is instantly converted into salts of the dye-base.

3. Aurines, Rosolic Acid Dyes

Compounds of this class possess a constitution similar to that of the true rosaniline dyes, although the nitrogen has been replaced by oxygen groups; they therefore bear the same relationship to phenol as the rosanilines bear to aniline. Hence they are not basic but weakly acidic

¹ These formulae only show that part of the molecule undergoing change.

dyes, which are, however, of much less value than those of the rosaniline series, since they are difficult to attach to the fabric. They are chiefly employed in the form of lakes in the paper and wall-paper industries. In these compounds the quinonoid structure is assumed so readily—even in the absence of mineral acid—that the corresponding carbinols are unknown.



Aurine, para-rosolic acid, may be obtained in the pure state from para-rospaniline by diazotisation and boiling the diazonium salt with water, when NH_2 is replaced by OH. Technically it is prepared by heating phenol with sulphuric acid and oxalic acid (the latter furnishing the "methane carbon atom"). It forms dark red rhombic crystals or red needles with a greenish lustre, dissolves in alkali to a fuchsine red solution, and has also weakly basic properties since it unites with acids. When heated to 150° with aqueous ammonia it yields para-rospaniline, and with nascent hydrogen it is reduced to *leucaurine*, trihydroxy-triphenylmethane, $\text{CH}(\text{C}_6\text{H}_4\cdot\text{OH})_3$. The latter is a colourless, crystalline compound which turns red in air or with oxidising agents, owing to the formation of aurine.

Rosolic acid, the quinonoid anhydride of *p*-trihydroxy-diphenyl-*m*-tolyl carbinol (formula, see above), is formed when the diazo-compound of rospaniline is boiled with water, or when a mixture of phenol and cresol is heated with arsenic acid and sulphuric acid (the methyl group of cresol provides the "methane carbon"). It forms crystals of greenish lustre which are insoluble in water and dissolve to a red solution in alkalis. With reducing agents rosolic acid is converted into *leuco-rosolic acid*, trihydroxy - diphenyl - tolylmethane, $(\text{HOC}_6\text{H}_4)_2\text{CH} \cdot \text{C}_6\text{H}_5(\text{CH}_3) \cdot \text{OH}$. When heated with water, rosolic acid breaks up into *p*-dihydroxyphenyl-tolyl ketone and phenol.

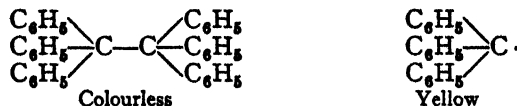
Triphenyl-methyl and Trivalent Carbon

The researches of Gomberg on triphenyl-methyl threw a new light on the problem of the valency of carbon (*cf.* p. 7). By treating a benzene solution of triphenyl-methyl chloride with zinc, silver or mercury in an atmosphere of CO_2 , Gomberg obtained a yellow solution which on evaporation deposited colourless crystals of *hexaphenyl-ethane*. In the

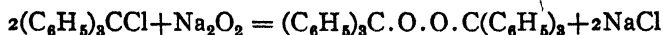


dissolved state the colourless hydrocarbon partially breaks down to yield an equilibrium mixture containing a yellow strongly unsaturated

compound, which is formulated as the free radical, **triphenyl-methyl**. Triphenyl-methyl was thus the first compound of trivalent carbon to be discovered.



Evidence that dissociation of the hexaphenylethane into triphenyl-methyl radicals had really occurred has been provided both by chemical and by physical methods. In contrast to hexaphenylethane the triphenyl-methyl radical will be highly unsaturated and this is shown by its behaviour towards various agents including oxygen and iodine. When a solution of the free radical is shaken with air, the yellow colour is immediately discharged, and oxygen is absorbed with production of a *peroxide*, whose structure follows from its synthesis from triphenylmethyl chloride and sodium peroxide.



If air is then excluded the colour rapidly reappears as more triphenylmethyl is regenerated by dissociation of some of the remaining hexaphenylethane. A solution of iodine is immediately decolorised by triphenylmethyl to form *triphenylmethyl iodide*, $(\text{C}_6\text{H}_5)_3\text{CI}$.

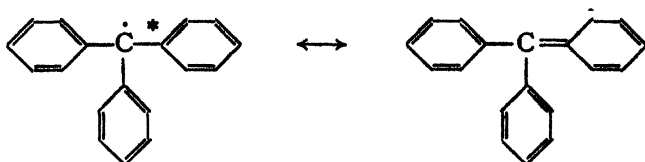
These and other chemical properties are quite different from those associated with ethane and its derivatives. The physical properties also are different from those expected. Not only does hexaphenylethane dissolve in benzene, etc. to give yellow solutions, but these solutions do not obey Beer's Law. In other words the equilibrium between hexaphenylethane and triphenylmethyl is dependent on the dilution of the solution.

The most conclusive evidence for the existence of free radicals comes from magnetic studies. A free radical differs from other substances in containing an unpaired electron in the molecule. The spin of this electron produces a magnetic field and in consequence the free radical is paramagnetic.¹ Free radicals thus differ fundamentally from almost all other organic substances which are diamagnetic. Magnetic susceptibility studies of solutions of hexaphenylethane and other related compounds have shown decisively the presence of free radicals. Further, by making use of the fact that hexaphenylethane is diamagnetic whilst triphenylmethyl is paramagnetic it is possible to calculate the degree of dissociation of the ethane into the free radical and this has been extended to a large number of hexa-arylethanes. These results have shown that while the parent compound, hexaphenylethane, in benzene dissociates only to a small extent into the free radical, other more highly substituted ethanes are largely or even completely dissociated. For example, *tri-diphenylmethyl*, $(\text{C}_6\text{H}_5 \cdot \text{C}_6\text{H}_4)_3\text{C}$, prepared by Schlenk, exists both in

¹ P. W. Selwood, *J. Chem. Education*, 1942, 19, 181.

solution and in the solid state in the monomolecular form. In benzene, for instance, its molecular weight is found to be between 434 and 487, in fair agreement with 471 required by the free radical. Its dissociation in the solid state is shown by the greenish-black colour of its crystals.

The question naturally arises why hexa-arylethanes dissociate into free radicals while ethane itself does not. The question may be posed in another form: why does the dissociation of hexaphenylethane into triphenylmethyl require only 11 Kcal. per mole whereas the dissociation of ethane into methyl radicals requires 85 Kcal. per mole. Two factors appear to cause the weakening of the carbon—carbon linkage in the hexa-arylethanes: a steric effect and resonance. It is reasonable to suppose that the volume of the aryl groups prevents the ethane carbon atoms approaching each other sufficiently closely to form a strong bond. For this there is considerable experimental evidence. Naphthyl groups, for example, result in a greater degree of dissociation than phenyl groups, and an α -naphthyl nucleus has a greater effect than a β -naphthyl nucleus. In the extreme example quoted above an ethane in which the six hydrogen atoms are replaced by the bulky diphenyl residues is completely dissociated into the free radical even in the solid state. The steric factor, however, is not the only one. This follows from the observation that *para*-substituents in the benzene rings can promote dissociation, hexa-*p*-tolylethane, for instance, being more dissociated than hexaphenylethane. It is probable indeed that the main factor responsible for the dissociation of hexaphenylethane and its analogues is not a steric but a resonance factor. In hexaphenylethane resonance occurs between the various Kekulé structures of the benzene rings. In the triphenylmethyl radical, however, the resonance results not only from the Kekulé structures but also from other structures in which the odd electron from the central carbon atom is distributed over the six ortho- and the three para-positions. The contributing form shown below, for example, may be supposed to result from the separation of two of the electrons constituting the double bond (marked*), followed by union of one of them with the odd electron on the central carbon atom. The other electron is retained on the ortho carbon atom of the ring.



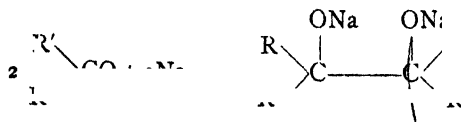
In the simple radical methyl, $\text{CH}_3\cdot$, the possibility of such a stabilising resonance does not exist and the structure is highly unstable.

Metallic Ketyls.—Another group of compounds containing trivalent carbon was discovered by Schlenk in the metallic ketyls of the general formula shown below. They are formed by the action of alkali metals on ketones, and are characterised by intense colour and great

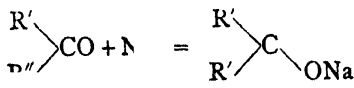
sensitiveness to oxygen. Trivalent carbon thus appears to betray itself in its strong chromophoric influence. In general, the interaction of an alkali metal and a ketone falls into one of the three following classes :

1. Where an enolic form can occur a metallic compound is produced with evolution of hydrogen, as in the case of acetone, which reacts as the enol $\text{CH}_2\text{:C(OH)CH}_3$.

2. The alkali metal may combine without evolution of hydrogen to form a saturated dimolecular compound :

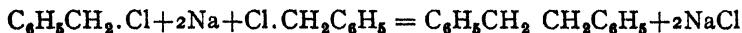


3. The alkali metal may combine directly to yield a metallic kety

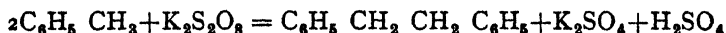


IV.—DIPHENYL-ETHANE GROUP

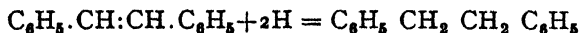
Dibenzyl, *s-diphenyl-ethane*, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, can be prepared by the action of copper or sodium on benzyl chloride,



by the oxidation of toluene with potassium persulphate,

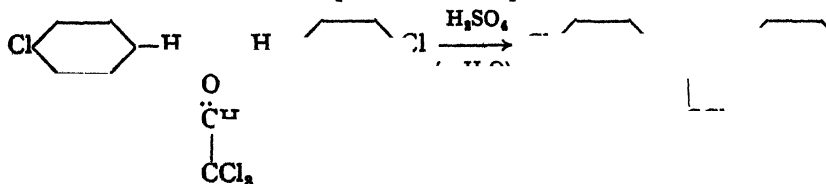


and by the reduction of stilbene with sodium and alcohol,



Pure dibenzyl, m.p. 52° , crystallises in elongated prisms ; but, when contaminated with stilbene as it often is, it crystallises in hexagonal prisms. This provides a good example of how the microscope may advantageously be used in ascertaining the purity of organic substances.

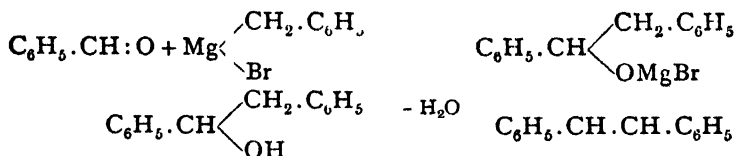
An important substance is 1:1-*bis*-(*p*-chlorophenyl)-2:2:2-trichloroethane (DDT) which is prepared by the condensation of chlorobenzene with chloral in the presence of sulphuric acid.



DDT has remarkable insecticidal properties and was used with unparalleled success in 1944 by the Allied authorities to arrest the outbreak of typhus in Naples.

The monthly production of DDT in America is estimated at 1,700,000 lb.¹

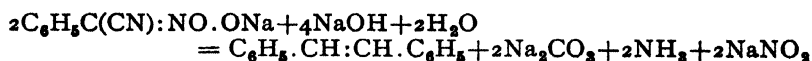
Stilbene, *s-diphenyl-ethylene*, $\text{C}_6\text{H}_5\cdot\text{CH}:\text{CH}\cdot\text{C}_6\text{H}_5$, is best prepared by the interaction of benzaldehyde and benzyl magnesium chloride, the carbinol first produced immediately parting with water.



Another method of preparing stilbene consists in heating an alkaline solution of phenyl-nitromethane.

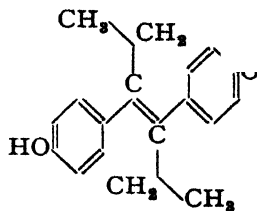


This may be much more readily effected by starting from the sodium compound of phenyl-nitro-acetonitrile, which is easily obtained from ethyl nitrate and benzyl cyanide.

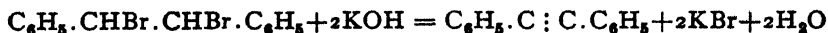


Stilbene crystallises in lustrous plates or prisms, m.p. 124° and b.p. 306° . It yields dibenzyl on reduction, and readily adds on halogens and hydrogen halides, *e.g.* with bromine it forms stilbene dibromide, $\text{C}_6\text{H}_5\cdot\text{CHBr}\cdot\text{CHBr}\cdot\text{C}_6\text{H}_5$.

trans-Diethyl-stilboestrol is one of the most potent oestrogens known,² and is employed as such in medicine (*stilbaestrol*, see inset formula). The control of cancer of the prostate by this substance is of great interest and gives rise to the hope that other forms of cancer may yield to similar treatment.

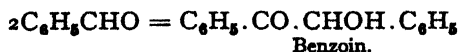


Tolane, *diphenyl-acetylene*, $\text{C}_6\text{H}_5\cdot\text{C}\equiv\text{C}\cdot\text{C}_6\text{H}_5$, is prepared from the above-mentioned stilbene dibromide by boiling with alcoholic potash. Tolane unites with two or four atoms of halogen and also with nitrogen peroxide. It melts at 60° .



Certain alcoholic and ketonic derivatives of dibenzyl are of interest.

Benzoin, a keto-alcohol of dibenzyl, is formed when benzaldehyde is warmed in alcoholic solution with potassium cyanide (*Benzoin condensation*).

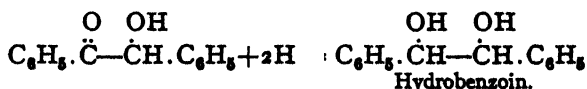


¹ See G. A. Campbell and T. F. West, *Chem. and Ind.*, 1944, 43, 319.
L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.*, 1939, B127, 140.

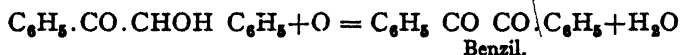
² E. C. Dodds,

This reaction is a general one, and may be carried out with other aldehydes of the same type as benzaldehyde. It is also reversible and by use of two different aromatic aldehydes mixed benzoin may be formed.

Benzoin crystallises in colourless, odourless prisms, m.p. 137°. It reacts both as a ketone and as a secondary alcohol. Thus it yields an oxime and a phenylhydrazone, and also ethers and esters. On reduction with sodium amalgam hydrobenzoin is formed.



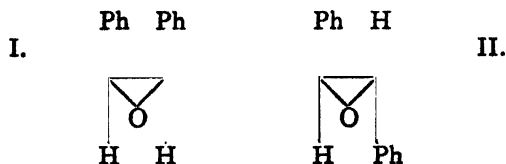
The presence of a secondary alcoholic grouping in benzoin is also shown by the behaviour of the compound on oxidation with nitric acid, when CHO is converted into CO with the production of benzil :



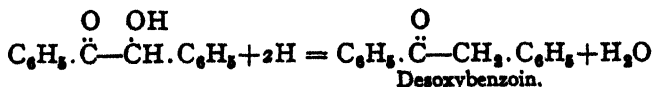
Benzoin contains an asymmetric carbon atom and its (+)- and (—)-forms were obtained by McKenzie and Wren.

Hydrobenzoin is prepared as described above. It contains two similar asymmetric carbon atoms and thus exhibits the same type of isomerism as tartaric acid. The reactions already quoted actually yield a variable mixture of the two inactive forms, *hydrobenzoin*, m.p. 134°, and *iso-hydrobenzoin*, m.p. 119°. Of these, the former is a meso-compound, whereas the latter is racemic and can be resolved into its two optically active components.

Stereoisomeric *diphenylethylene oxides* have been prepared from hydrobenzoin by Read.¹ The symmetrical compound I is inactive, but the dissymmetrical oxide II exists in a racemic form and in two optical isomers of high activity.



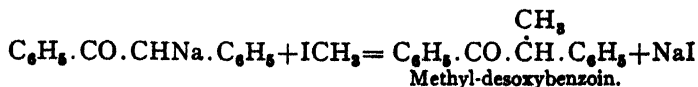
If benzoin is reduced with zinc and alcoholic hydrochloric or acetic acid, instead of with sodium amalgam, the alcoholic group alone is attacked and desoxybenzoin formed.



Desoxybenzoin, *benzyl phenyl ketone*, m.p. 60°, is prepared by the above method, and by the usual methods for preparing aromatic ketones,

¹ J. Read and I. G. M. Campbell, *J.*, 1930, 2377.

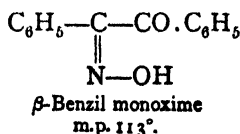
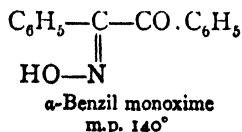
e.g. from phenyl-acetyl chloride, $C_6H_5 \cdot CH_2 \cdot COCl$, and benzene in the presence of aluminium chloride. On energetic reduction it yields dibenzyl. Desoxybenzoin resembles aceto-acetic ester in that one hydrogen atom of the methylene group is replaceable by sodium and alkyl groups.



The prefix *desoxy* signifies that a secondary alcohol group has been converted into a methylene group.

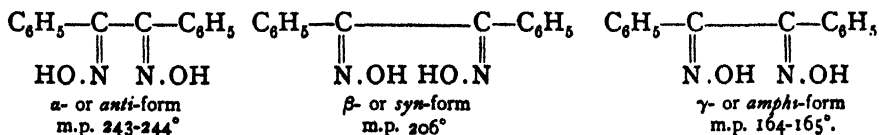
Benzil forms yellow prisms, m.p. 95° . Owing to the ease with which it is prepared from benzoin, it is one of the most accessible of the α -diketones. Among its derivatives the oximes are of special interest, since the study of these compounds has contributed largely to our knowledge of the stereochemistry of the nitrogen atom.

Two monoximes and three dioximes of benzil are known. An examination of the chemical behaviour of the monoximes has led to them being assigned the following space formulæ :

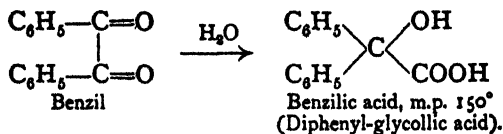


For methods of determining the configuration of the stereoisomeric ketoximes, see p. 53.

The configurations of the three isomeric benzil-dioximes are now written as follows, involving a transposition of the formulæ previously ascribed to the α - and β -forms¹ :



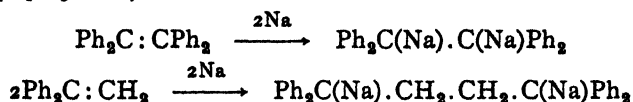
A peculiar property of benzil is the change it undergoes when heated with alcoholic potash, when an intramolecular rearrangement takes place with the formation of *benzilic acid* :



¹ J. Meisenheimer, *Ann.*, 1929, 469, 130. In accordance with a proposal of Hantzsch the terms *syn*-, *anti*- and *amphi*- are employed in the sense indicated in the above formulæ in describing the stereoisomeric dioximes. (See also general notes in the chapter on "Stereochemistry.")

This reaction resembles the conversion of phenanthraquinone into diphenylene-glycollic acid (p. 521), and of β -naphthaquinones into oxindene-carboxylic acids.

Hydrocarbons containing phenyl groups linked to unsaturated carbon have the property of uniting directly with alkali metals,¹ as in the following examples ($C_6H_5 = Ph$).

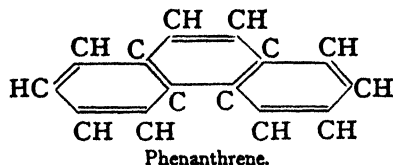
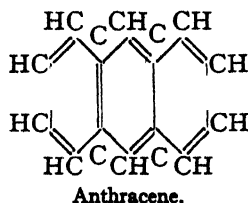
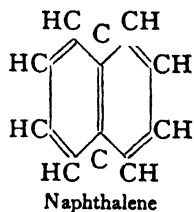


A similar addition is observed with certain hydrocarbons in which unsaturated carbon is linked to other unsaturated groups.

XV

Condensed Polynuclear Compounds

Under this heading are described compounds containing several benzene nuclei linked together in such a manner that each pair possesses two carbon atoms in common, as in the following formulæ.



These hydrocarbons, like benzene, are found in coal tar, and as might be expected are on the whole aromatic in character.

Naphthalene Group

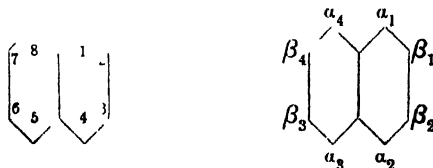
Naphthalene, $C_{10}H_8$, is obtained from the fraction of coal tar known as "middle or carbolic oil," boiling between 170° and 240° (see p. 428). The crystals which deposit from the oil on cooling are separated under pressure from liquid impurities, and further purified by heating with a small amount of sulphuric acid and subsequent sublimation. Naphthalene forms shining white rhombic leaflets of an unpleasant, penetrating smell and burning taste. It melts at 79° , boils at 218° and very readily sublimes.

¹ W. Schlenk and E. Bergmann, *Ann.*, 1928, 463, 1, 98.

a double bond. The reactivity of the halogen atom in *o*- and *p*- but not in *m*-bromonitrobenzene can be traced to the same cause. In the naphthalene series it is found that the bromine atom in 1-bromo-2-nitronaphthalene is reactive towards piperidine whereas 3-bromo-2-nitronaphthalene is quite inactive.¹ We thus again have evidence of the double bond character of the 1 : 2-linkage and the single bond character of the 2 : 3-linkage. From these and other chemical investigations it is concluded that naphthalene is satisfactorily represented by the Erlenmeyer formula modified in terms of resonance (formula IV).

Isomerism of Naphthalene Derivatives

From the formula for naphthalene it is possible to predict the existence of a number of isomeric substitution products. In order to indicate the position of substituent atoms or radicals, use is made of one or other of the following systems :



It will be seen that even the mono-derivatives of naphthalene can exist in two series, according to whether or not the substituent is attached to an atom adjacent to one of the two carbon atoms common to both rings. Those compounds formed by the replacement of one of the four equivalent hydrogen atoms 1, 4, 5, or 8 are known as α -compounds, and those obtained by substituting one of the four equivalent atoms 2, 3, 6, or 7 as β -compounds. Whether a radical is attached in the α - or β -position can frequently be determined by oxidising the substance under consideration to the corresponding phthalic acid derivative (*cf.* p. 569).

A disubstitution product of naphthalene may occur in 10 isomerides if the two substituents are similar, or in 14 isomerides if they are different. With the entry of more than two atoms or groups into the molecule the number of isomerides is very much larger.

Compounds in which two substituents are attached to two adjacent carbon atoms correspond in their behaviour to the ortho-derivatives of the benzene series. Similar behaviour with respect to anhydride formation and condensation is also shown by 1 : 8- or 4 : 5-derivatives, these positions being known as *peri*-positions. *Peri*-derivatives possess in an enhanced degree the properties characteristic of *o*-compounds. This may be seen from a comparison of *peri*-amino-naphthoic acid with anthranilic acid, of naphthalic with phthalic acid, and of 1 : 8-naphthylene-diamine with *o*-phenylene-diamine. In all cases where *o*-diamines are able to take up

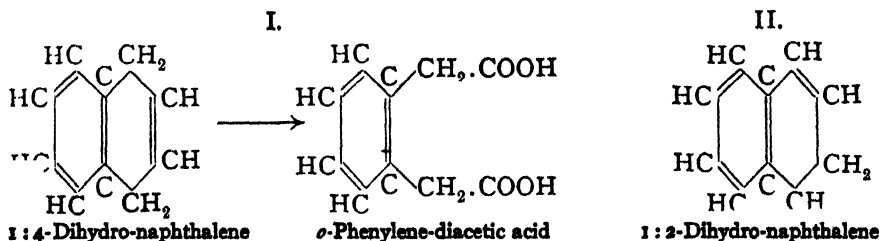
¹ N. McLeish and N. Campbell, *J.*, 1937, 1103.

a new element to form a five-membered ring-system, the *peri*-diamines can similarly form a six-membered ring. In the latter case, however, the reaction occurs much more readily than with the *o*-derivatives.

Chemical Behaviour of Naphthalene

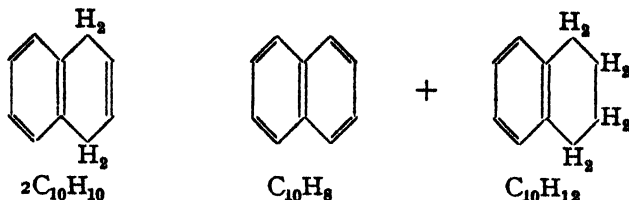
As already stated, naphthalene shows in general the properties characteristic of aromatic compounds. It reacts with halogens, nitric acid, and sulphuric acid in a manner similar to benzene with the formation of chloro-, nitro-, and sulphonic derivatives. These products are described on p. 576 *et seq.* Further evidence of the aromaticity of naphthalene is furnished by its formation of addition compounds with picric acid, 1 : 3 : 5-trinitrobenzene, 2 : 4 : 7-trinitrofluorenone, etc. The formation of these "picrates", etc. is a characteristic feature of polycyclic aromatic hydrocarbons. The addition or molecular compounds are formed from chemical substances, each of which is capable of a separate existence, and the mode of combination is by no means obvious. The stable naphthalene and picric acid molecules, for example, combine to form the stable, crystalline addition product, generally but erroneously termed *naphthalene picrate*. The addition compounds are frequently used for identification and purification, since they crystallise well and have sharp melting-points.

With ozone naphthalene forms an explosive, crystalline diozonide in which two molecules of ozone are attached to one of the benzene nuclei. In some ways, however, naphthalene differs from benzene, particularly in the ease with which it is hydrogenated and oxidised under conditions in which benzene remains unattacked. In other words naphthalene is less saturated than benzene. When reduced with sodium in boiling ethanol it yields 1 : 4-dihydronaphthalene, $C_{10}H_{10}$, m.p. 15° , b.p. 212° . Oxidation of the compound affords *o*-phenylene-diacetic acid (I), thus proving that the hydrogen atoms have assumed the 1 : 4-positions.



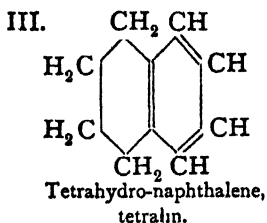
1 : 4-Dihydronaphthalene resembles ethylene in its unsaturated properties and adds on bromine, hydrogen, etc., at the 2- and 3-positions. On the other hand it possesses the tendency characteristic of partially hydrogenated aromatic systems to undergo *aromatisation*, as shown by its decomposition merely on heating to give naphthalene and hydrogen, or by its *disproportionation* into naphthalene and 1 : 2 : 3 : 4-tetrahydronaphthalene when heated with hydrogenation catalysts such as palladium.

If 1:4-dihydronaphthalene is heated to 140° with 5 per cent. sodium ethoxide, the position of the double bond is shifted with the formation



of 1:2-dihydronaphthalene, Δ^1 -dihydronaphthalene (II), m.p. -7° . The constitution of this compound is shown by the production of hydrocinnamic-*o*-carboxylic acid on oxidation with permanganate.

Reduction of naphthalene with sodium in a high boiling alcohol such as isoamyl alcohol yields 1:2:3:4-tetrahydronaphthalene, tetralin (III), which is prepared industrially by the catalytic reduction of naphthalene.



In the technical preparation, naphthalene is first fused with finely-divided metals of low melting-point in order to remove sulphur and other substances, which would "poison" the catalyst used in subsequent operations. The purified naphthalene is then placed in an autoclave provided with stirring apparatus and treated with hydrogen under pressure, in the presence of a nickel salt. The reaction slows down after four atoms of hydrogen have been taken up. As the change is exothermic heat need only be supplied to start the reaction.

The tetralin of commerce is a colourless liquid, b.p. 206° - 208° . Pure tetralin (b.p. 206.5° at 755 mm. pressure) is obtained from the sulphonic acid by the action of superheated steam. Tetralin is a good solvent for sulphur, fats, resins, and many other organic products, and hence is employed industrially as a solvent in the preparation of varnishes and lacquers, and admixed with benzene and alcohol as a fuel for internal combustion engines.

When tetralin is treated with bromine it behaves in the same manner as an alkyl benzene. In the cold, no reaction takes place in the absence of light; but on the addition of a little iron or a trace of iodine, substitution readily occurs in the benzene nucleus, even at -10° , with the formation of a mixture of 5- and 6-bromo-1:2:3:4-tetrahydronaphthalenes. Under the action of light or at a higher temperature in the absence of catalysts, halogen attacks the reduced ring.

Naphthalene on substitution gives almost exclusively α -compounds (see below) and the corresponding β -products are generally obtained

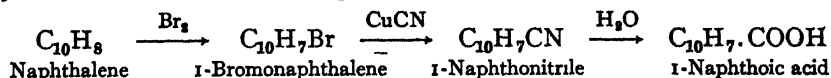
only by indirect and sometimes troublesome methods. Tetralin, on the other hand, when substituted in the aromatic ring gives a mixture of α - and β -compounds. Nitration, for example, gives equal quantities of 5- and 6-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene which can be separated by fractionation. The 6-nitro-compound can readily be dehydrogenated to give 2-nitronaphthalene, which is otherwise not easily prepared. Other reactions, particularly the entrance of carboxyl and acyl groups under the influence of aluminium chloride, proceed almost completely in the direction of the β -compounds; whilst with naphthalene the same conditions frequently furnish a difficultly separable mixture of α - and β -products. Here again 2-substituted naphthalenes may be obtained by dehydrogenation.

Oxidation of naphthalene yields either α -naphtha-quinone (p. 584) or phthalic anhydride according to the oxidising agent and the conditions used. It will be noted that benzene cannot be oxidised directly to benzoquinone.

Decahydro-naphthalene, decalin, $C_{10}H_{18}$, is prepared from tetralin, by further hydrogenation with fresh catalyst under 12 to 15 atmospheres pressure. It boils at 189° to 191° . D_4^{18} 0.8842. Huckel showed that decalin exists in a *cis*-form and a *trans*-modification (see p. 587).

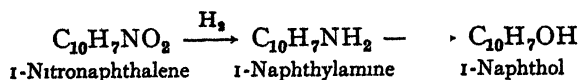
SUBSTITUTION PRODUCTS OF NAPHTHALENE

Naphthalene is a typical aromatic compound, like benzene readily undergoing nitration, halogenation, sulphonation, etc. These substitution reactions obey the so-called alpha law which states that electrophilic attack occurs almost entirely at the α -position in the naphthalene molecule. Substitution occurs more readily than in benzene. Bromine, for instance, attacks naphthalene so easily that the reaction may be used to obtain a steady flow of hydrogen bromide. It will be remembered that bromine attacks benzene only in the presence of a catalyst. Nitration also occurs mainly at the α -position. There is thus no difficulty in preparing α -naphthalene derivatives, especially since 1-bromo- and 1-nitronaphthalene can be converted into other compounds by means of reactions already discussed in the benzene series. A few of the products obtained in this way are shown in the following chart.



HNO_3

diazo



That these compounds are indeed 1- or α -derivatives of naphthalene is proved by their relationship to 1-naphthol, whose structure was proved by synthesis (p. 570).

For the preparation of 2- or β -substituted naphthalenes use is made of

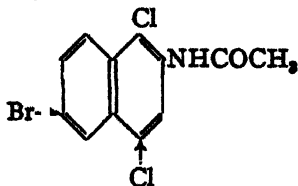
certain properties of naphthalene and tetralin, in particular the dehydrogenation of the readily accessible β -derivatives of tetralin (see above); the sulphonation of naphthalene under certain conditions to give naphthalene-2-sulphonic acid; and the formation of β -products in the Friedel-Crafts reaction by the use of specific solvents. These reactions are discussed later.

The further substitution of monosubstituted naphthalenes is considerably more complicated than with the corresponding monosubstituted benzene derivatives. This is partly because the number of products is greater—there are three dichlorobenzenes and ten dichloronaphthalenes; and partly because the products obtained are often more susceptible to the conditions and reagents used. Consequently the rules which have been derived for the formation of polysubstituted naphthalenes must be used with some caution.¹

A substituent, which in the benzene ring directs to the ortho and para positions, gives rise to further substitution mainly in the ring to which it is attached. This is clearly shown by 1-methylnaphthalene, which on nitration gives mainly 4-nitro-1-methylnaphthalene (70 per cent. yield), with much smaller amounts of the 2-, 5-, and 8-isomers.² 1-Chloronaphthalene with chlorosulphonic acid yields the 4-sulphonic acid. 2-Chloronaphthalene, however, with chlorosulphonic acid in carbon disulphide gives mainly the 8-sulphonic acid together with a little of the 6-isomer, and there are other exceptions to the rule.

Meta-directing substituents yield products substituted in the second ring. 1-Nitronaphthalene with chlorosulphonic acid yields 1-nitronaphthalene-5-sulphonic acid, and 1-naphthalenesulphonic acid likewise gives 1 : 5-naphthalene disulphonic acid.

The products obtained when naphthalene undergoes substitution frequently depend on the temperature of the reaction. This is particularly the case with the sulphonic acids since α -sulphonic acids tend to change into the β -acids (see below). In the example given above of the sulphonation of 2-chloronaphthalene a rise in temperature of the reaction increases the yield of the 2-chloro-6-naphthalenesulphonic acid at the expense of the 8-acid. Another example of isomerisation is found in the conversion of 1 : 8-dichloronaphthalene into 1 : 5-dichloronaphthalene by heating with hydrochloric acid at 290°.



Chlorine and bromine sometimes show an unexpected difference in

¹ See the H. E. Armstrong obituary notice by E. H. Rodd, *J.*, 1940, 1421. ² H. W. Thomson, *J.*, 1932, 2310.

attacking naphthalene derivatives.¹ For example, 1-chloro-2-aceto-naphthalide chlorinates in position 4, but brominates in position 6. It is thus obvious that the orientation of naphthalene derivatives must be rigidly established.

(a) Homologues

α-Methyl-naphthalene, $C_{10}H_7 \cdot CH_3$, m.p. -20° , b.p. 240° to 243° , and *β-methyl-naphthalene*, m.p. 32.5° , b.p. 241° to 242° , are found with dimethyl-naphthalenes in coal tar. Synthetically they may be prepared by methods similar to those employed for the benzene homologues, such as by treating the bromo-naphthalenes with alkyl halides and sodium, and by the Friedel-Crafts reaction from alkyl iodides or bromides and naphthalene in the presence of aluminium chloride.

(b) Halogen and Nitro-derivatives

As already mentioned, the action of chlorine or bromine on the hydrocarbon yields *α*-substitution products. The *β*-halogen compounds are best prepared from the hydroxy-, amino- or sulphonic derivatives by replacing the substituent with halogen according to methods described under benzene. The halogen atoms in these derivatives are less difficult to remove than those in the corresponding benzene compounds, but are nevertheless far more firmly attached than in the alkyl halides, and cannot be exchanged by boiling with aqueous alkalis.

1-Chloronaphthalene, $C_{10}H_7Cl$, boils at 263° . It is formed by the chlorination of boiling naphthalene, but is best prepared from *α*-aminonaphthalene by way of the diazo-compound. **1-Bromonaphthalene** is prepared by the bromination of naphthalene and since it yields Grignard reagents readily it is a very useful starting material for the synthesis of 1-naphthalene derivatives. It also yields **1-naphthonitrile**, when heated with cuprous cyanide in pyridine (*Rosenmund—von Braun Reaction*).



The nitration of naphthalene with concentrated nitric acid at ordinary temperature leads mainly to the formation of **1-nitronaphthalene** (95.5 per cent.), and a little of the *β*-isomer (4.5 per cent.). It crystallises in yellow needles; m.p. 61° , b.p. 304° . The orientation of 1-nitronaphthalene has already been discussed. Since the nitro-group can be exchanged by the usual methods for a variety of atoms and radicals, 1-nitronaphthalene has frequently been of aid in determining the position of the substituent in mono-derivatives of naphthalene. It is used industrially in the preparation of *α*-naphthylamine.

β-Nitro-naphthalene m.p. 79° , is prepared from technical *β*-naphthylamine by diazotisation in nitric acid solution and treating the naphthalene

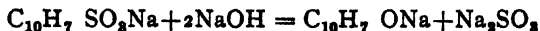
¹ F. Bell, *J.*, 1953, 3035.

diazonium nitrate with cuprous oxide; by decomposition of β -naphthalene diazonium cobaltinitrite¹; or from β -nitro-tetralin by dehydrogenation with the aid of bromine.

(c) Naphthalene Sulphonic Acids, Naphthols, Naphthylamines

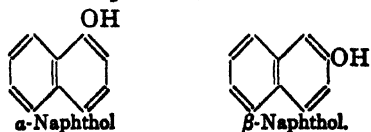
When heated with concentrated sulphuric acid, naphthalene always gives a mixture of the two isomeric naphthalene-sulphonic acids, $C_{10}H_7 \cdot SO_3H$; below 100° more of the α -form is produced and above 160° more of the β -compound. These reactions are reversible, in the sense $C_{10}H_7 \cdot SO_3H + H_2O \rightleftharpoons C_{10}H_8 + H_2SO_4$. The α -acid, however, is hydrolysed to naphthalene many times more rapidly than the β -compound, and this difference between the two forms becomes more pronounced with rise in temperature and with increasing concentration of sulphuric acid.² Consequently, higher temperatures and stronger sulphuric acid favour the production of naphthalene β -sulphonic acid.

The α - and β -sulphonic acids are deliquescent crystalline solids, the sodium salts of which on being fused with caustic alkali yield the corresponding naphthols:



On the large scale one part of sodium naphthalene-sulphonate is melted under pressure at about 300° with a concentrated solution of two parts of sodium hydroxide in iron vessels provided with stirring apparatus. From the sodium naphtholate so formed, naphthol may be precipitated by means of sulphuric acid or carbon dioxide, and purified by distillation alone or with superheated steam.

α -Naphthol, m.p. 96° , crystallises in needles. Owing to the difficulty of preparing sodium naphthalene- α -sulphonate free from the β -compound, α -naphthol is best obtained from α -naphthylamine by hydrolysis with 10 per cent. sulphuric acid at 200° . For a synthesis see p. 570. β -Naphthol, m.p. 122° and b.p. 286° , forms leaflets; it is prepared by



alkali fusion of sodium naphthalene- β -sulphonate. In chemical behaviour the naphthols show a general resemblance to the phenols, although the hydroxyl groups are much more reactive than in the latter compounds. They form ethers when heated with alcohols and sulphuric or hydrochloric acid. Most phenols are not alkylated in this way. They are also smoothly converted into naphthylamines by the Bucherer reaction (p. 581). Phenols on the other hand are converted into amines only by heating at a high temperature with ammonia and a catalyst such as zinc chloride.

The two naphthols differ in their behaviour on reduction with sodium and alcohol. In the case of α -naphthol the four hydrogen atoms almost

¹ Hodgson and Marsden, *J.*, 1944, 22.

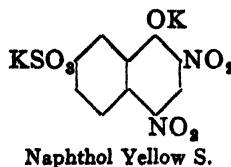
² R. Lautz, *Bull. Soc.*, 1935, [v], 2, 202a.

exclusively enter the hydroxyl-free ring to form *ar*-tetrahydro- α -naphthol,¹ (C_4H_8): $C_6H_5.OH$, which possesses the character of a true phenol. With β -naphthol the four hydrogen atoms not only enter the hydroxyl-free ring to give *ar*-tetrahydro- β -naphthol, (C_4H_8): $C_6H_5.OH$, but also that containing the $-OH$ group to form *ac*-tetrahydro- β -naphthol, ($HO.C_4H_7$): C_6H_5 . The first of these resembles the phenols in properties, and the latter the aliphatic alcohols. These interesting differences are discussed in more detail under the naphthylamines.

A large number of ethers, sulphonic acids and nitro-derivatives of the naphthols have been prepared. The hydroxy-derivatives of the naphthalene series also resemble the phenols in reacting in tautomeric forms.

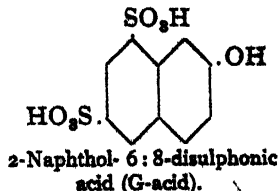
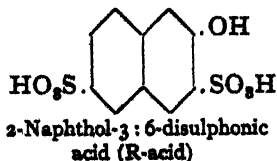
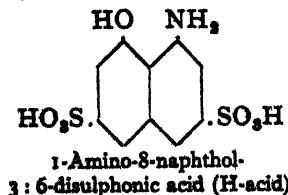
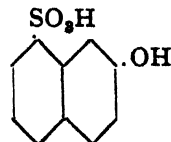
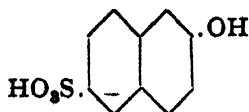
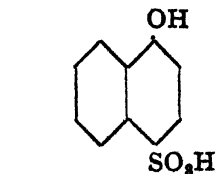
β -Naphthyl methyl ether, $C_{10}H_7.OCH_3$, m.p. 72° , is obtained by heating β -naphthol with methyl alcohol and hydrochloric acid, or by heating sodium β -naphtholate with dimethyl sulphate. It has a smell like oil of orange flowers (neroli oil), and is used under the name of *nerolin* in the preparation of perfumes.

Dinitro- α -naphthol, $C_{10}H_5(NO_2)_2OH$, [$OH.NO_2^1.NO_2^4$], is prepared by treating α -naphthol-disulphonic acid (1 : 2 : 4) with nitric acid, and crystallises in needles, m.p. 138° . It is almost insoluble in water but its salts are comparatively soluble, the sodium or less frequently the potassium compound being placed on the market under the name of **Martius yellow**. In an acid bath it dyes wool and silk a golden yellow colour. **Naphthol yellow S**



is the potassium or sodium salt of the sulphonic derivative of dinitro- α -naphthol. It is a more permanent dye than Martius yellow.

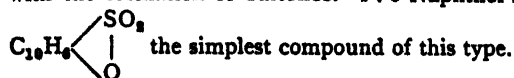
Naphthol-sulphonic acids are produced either by direct sulphonation, by fusing polysulphonic derivatives of naphthalene with alkali hydroxide, or by replacing the NH_2 -group in naphthylamine sulphonic acids with the hydroxyl group. They are extensively used in the dyeing industry.



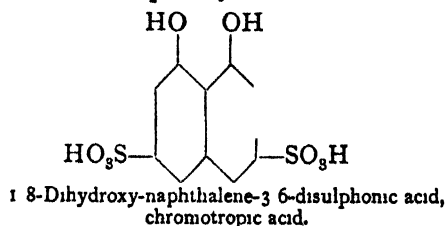
¹ For the use of the prefixes *ar*- and *ac*- see p. 583

Among the numerous sulphonic acids of the naphthols those named above are the ones chiefly used in the preparation of azo-dyes. Nevile and Winther's acid and *disulphonic acids H, R and G* are of particular value. The two last are formed by the vigorous sulphonation of β -naphthol and can be separated by taking advantage of the different solubilities of their acid sodium salts in alcohol, that of the G-acid being readily soluble and that of the R-acid almost insoluble. Whereas 2-naphthol-8-sulphonic acid and G-acid generally yield yellowish dyes when coupled with diazonium compounds, Schaffer's acid and R-acid give bluish dyes.

Sulphonic acids of α -naphthol containing hydroxyl and sulphonic groups in the *peri*-positions (1 : 8) very readily split off water between the SO_3H and OH groups, with the formation of *sultones*. 1 : 8-Naphthol-sulphonic acid yields *naphtha-sultone*,



A number of isomeric dihydroxy-naphthalenes are known, among which *peri*-dihydroxy-naphthalene may be specially noted, since in consequence of the adjacent position of the two hydroxyl groups it resembles *o*-dihydroxy compounds in forming mordant dyes. This property is utilised in azo-dyes prepared from a disulphonic acid of *peri*-dihydroxy-naphthalene, which are classed together under the name of *chromotrope* dyes. The acid itself is consequently termed *chromotropic acid*.



The colours produced with azo-dyes derived from this acid undergo surprising variations with change of metallic mordant. For example, the dye prepared from diazotised aniline dyes wool in acid bath a red colour. Aluminium salts transform this colour to violet and chromates to blue-black.

α - and β -Naphthylamines, $\text{C}_{10}\text{H}_7\text{.NH}_2$, can be prepared by reducing the corresponding nitro-compounds and this method is used on the technical scale for the preparation of the α -compound, the reducing agent being iron and hydrochloric acid. *α -Naphthylamine*, m.p. 50° , b.p. 300°C. , possesses an unpleasant odour and is readily attacked by oxidising agents.

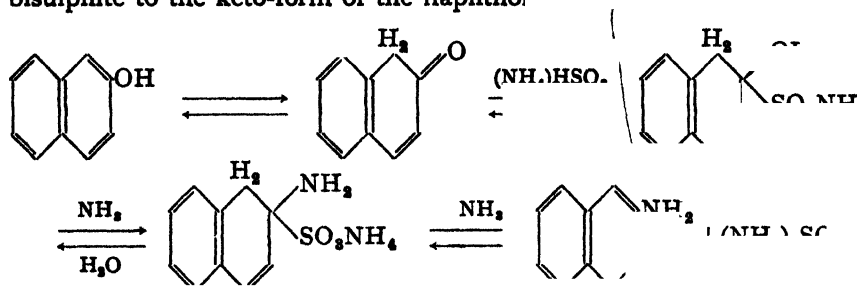
The above method is unsuitable for the large scale production of *β -naphthylamine* (m.p. 112°) as β -nitronaphthalene is not readily obtainable. It is manufactured by the method of Bucherer.¹ This reaction is the reversible conversion of a naphthol to a naphthylamine

¹ *The Bucherer Reaction*, Nathan L. Drake in *Organic Reactions* (Editor, Roger Adams), vol. 1, p. 105. N. Campbell, *Ann. Reports*, 1948, 44, 138.

in presence of ammonium sulphite or bisulphite, and is applicable with only a few exceptions to members of the naphthalene series. For example β -naphthol gives an excellent yield of β -naphthylamine on treatment with ammonium bisulphite.



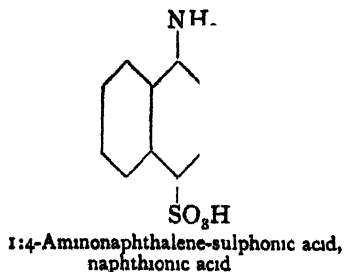
The most probable mechanism of the reaction involves addition of bisulphite to the keto-form of the naphthol



The naphthylamines and their sulphonic acids are largely employed in the manufacture of azo-dyes (see p. 487).

Substituted naphthylamines can be prepared by a variety of methods. 2-Naphthylamine, for example, in sulphuric acid solution brominates to give 1:6-dibromo-2-naphthylamine. The position occupied by a substituent, however, may be varied by altering solvents, etc. 2-Toluene-*p*-sulphonamidonaphthalene on bromination yields the 1-bromo-product, which on further bromination in acetic acid gives 1:6-dibromo-2-toluene-*p*-sulphonamidonaphthalene, but in pyridine gives the corresponding 1:3-dibromo derivative.¹ Substituted naphthylamines may also be prepared by indirect methods. This is exemplified by the conversion of the readily accessible 8-bromo-1-naphthoic acid (p. 586) into 8-bromo-1-naphthylamine by means of the *Schmidt* reaction.²

On treatment with fuming sulphuric acid, α -naphthylamine yields **naphthionic acid** (formula see below), which corresponds to sulphanilic

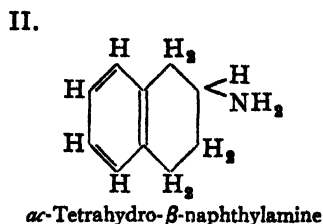
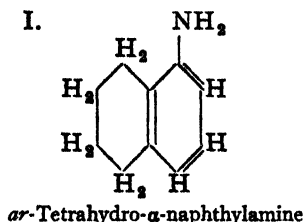


¹ F. Bell, *J.*, 1932, 2733.

² N. Campbell and A. A. Woodham, *J.*, 1953, 843.

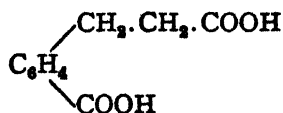
acid. When this compound is diazotised and coupled with β -naphthol, it is converted into fast red A. Naphthionic acid coupled with tetrazobenzidine chloride forms Congo red (see p. 491).

Both naphthylamines are reduced by sodium and amyl alcohol to tetrahydronaphthylamines, all four hydrogen atoms entering the same benzene nucleus. The products so obtained, however, show striking differences in properties. The tetrahydro-1-naphthylamine (I) behaves very much like aniline. It has a characteristic odour, undergoes diazotisation, etc. and must therefore have undergone reduction entirely in the unsubstituted nucleus. Its formula is thus 5:6:7:8-tetrahydro-1-naphthylamine (I), and it is frequently termed *aromatic*- or *ar*-tetrahydro-



1-naphthylamine. The tetrahydro-2-naphthylamine on the other hand exhibits the characteristics of an aliphatic amine. It has an ammoniacal odour resembling that of piperidine; with nitrous acid it does not form a diazonium salt but yields instead a stable nitrite, etc. Obviously hydrogenation has occurred in the ring containing the amino-group, and this type of reduction is distinguished as aliphatic-cyclic or *alicyclic hydrogenation*. The compound formed is 1:2:3:4-tetrahydro-2-naphthylamine (II) or *ac*-tetrahydro-2-naphthylamine.

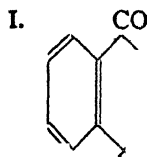
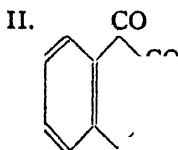
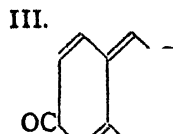
That the hydrogen atoms always attach themselves asymmetrically, *i.e.* to *one* of the two nuclei of the naphthalene molecule, was proved by Bamberger from an examination of the behaviour of the compounds towards bromine and potassium permanganate. The above reduction products do not add on bromine. Had each nucleus taken up two hydrogen atoms, derivatives containing double bonds would have been formed which would have combined instantaneously with bromine. The products obtained by the oxidation of the two compounds are such as would be expected from the formulæ assigned. 5:6:7:8-Tetrahydro-1-naphthylamine yields adipic acid, $\text{COOH}(\text{CH}_2)_4\text{COOH}$, and 1:2:3:4-tetrahydro-2-naphthylamine affords *o*-carboxy-hydrocinnamic acid,



In general it may be said that aromatic rings on reduction lose their characteristic properties and acquire the functions of an open aliphatic chain.

(d) Naphthaquinones and Naphthalene Carboxylic Acids

Three quinones of naphthalene are known, namely,

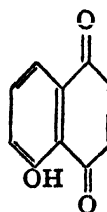
 α -Naphthaquinone β -Naphthaquinone

para-Naphthaquinone

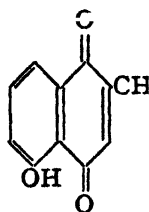
α -Naphthaquinone corresponds to *p*-benzoquinone. It is prepared by oxidising naphthalene with chromic acid in boiling glacial acetic acid. Better yields are obtained by oxidation of 1:4-dihydroxy-naphthalene or of 1:4-aminonaphthol. It is also formed when naphthalene, dissolved in acetone containing sulphuric acid, is electrolytically oxidised at a platinum or lead anode. In its properties it strongly resembles quinone. It crystallises from alcohol in yellow needles, m.p. 125° , has a pungent smell and is very volatile. Sulphurous acid reduces it to 1:4-dihydroxy-naphthalene, and with nitric acid it is oxidised to phthalic acid.

Natural Naphthaquinone Pigments.—Some naturally occurring pigments are derivatives of α -naphthaquinone, and the discovery that vitamins K_1 and K_2 belong to this group is of great physiological interest.

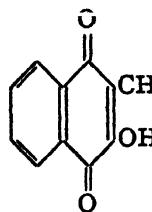
Three of the simplest naturally occurring naphthaquinones are *juglone*, *plumbagin*, and *phthoicol*.



Juglone

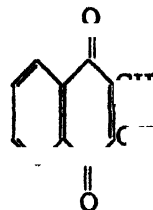
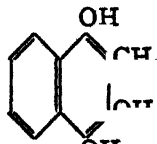
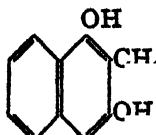


Plumbagin



Phthoicol

Phthoicol³ is of special interest as it is the yellow pigment of human tubercle bacilli. It is readily synthesised by oxidation of 2-methyl-1:3-dihydroxynaphthalene in alcoholic potassium hydroxide solution with atmospheric oxygen.³

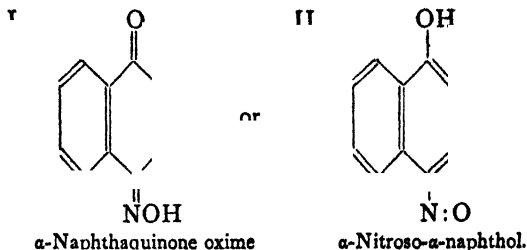


Phthoicol.

¹ R. D. Haworth, *Ann. Reports*, 1939, 278. A. R. Todd, *ibid.*, 1941, 38, 207. ² R. J. Anderson and M. S. Newman, *J. Biol. Chem.*, 1933, 103, 405. ³ Gabra Soliman and A. Latif, *J.*, 1944, 55.

β -Naphthaquinone, which may be compared to *o*-benzoquinone, results from the oxidation of 1:2-amino-naphthol. It crystallises in red needles which decompose about 120°. It differs from the α -compound in being odourless and non-volatile. In chemical behaviour it resembles anthraquinone and even more closely phenanthraquinone. As will be seen later, the reactions of the latter are those of an ortho-diketone. Sulphurous acid reduces β -naphthaquinone to 1:2-dihydroxy-naphthalene.

When treated in alcoholic solution with hydroxylamine hydrochloride the naphthaquinones are converted into *naphthaquinone monoximes*.



These are identical with the compounds obtained by the action of nitrous acid on the naphthols, hence they may also be considered as *nitroso-naphthols*. Here we have a case of tautomerism analogous to that of the nitrosophenols. The α -quinone only yields one monoxime.

The two monoximes of β -naphthaquinone differ from the oxime of α -naphthaquinone in their ability to act as mordant dyes, forming dark green lakes with ferric oxide. In particular, the iron salt of α -nitroso- β -naphthol-sulphonic acid is employed in wool-dyeing under the name of *Naphthol Green*. α -Nitroso- β -naphthol precipitates various metals from their solutions, yielding, for example, a sparingly soluble cobaltic compound which may be utilised in separating nickel and cobalt.

Amphi-naphthaquinone (formula, see p. 584) is formed when 2:6-dihydroxy-naphthalene, suspended in benzene, is oxidised with lead peroxide.¹ It crystallises in small yellowish red prisms and is very unstable towards water, alcohol, acids and alkalis. In physical properties it resembles the *o*-quinones. Like the benzoquinones, it is distinguished by a tendency to change into the benzenoid type.

The *amphi*-compound differs from α - and β -naphthaquinones in its far stronger oxidising action. It is truly naphthaquinonoid, whereas the α - and β -isomerides are not completely quinonoid in structure. Here a distinction is drawn between quinones in which the benzene ring or condensed double ring of naphthalene is completely quinonoid and those in which a quinonoid double bond is also part of an aromatic nucleus.

Naphthalene-carboxylic acids.—In formation and properties the naphthalene-carboxylic acids resemble the corresponding acids of benzene, to which reference should be made. 1-Naphthoic acid, naphthalene-1-carboxylic acid, $C_{10}H_7 \cdot COOH$, m.p. 160°, is formed by the action of

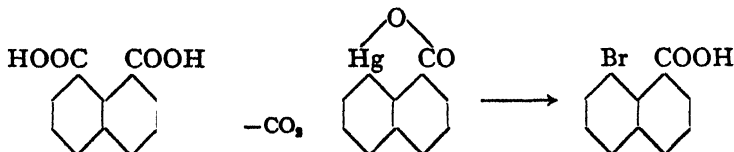
¹ R. Willstätter and Parnas, *Ber.*, 1907, 40, 1406.

carbon dioxide on naphthylmagnesium bromide. **2-Naphthoic acid** can be obtained from 2-naphthonitrile, which is obtained only in poor yield from 2-naphthylamine by the diazo-reaction. The readily accessible *Tobias acid*, however, 2-aminonaphthalene-1-sulphonic acid, gives nearly a quantitative yield of the 2-cyano compound, which when heated with



dilute sulphuric acid gives 2-naphthonitrile (85 per cent. yield based on the Tobias acid). Hydrolysis then gives 2-naphthoic acid, m.p. 182°.


Naphthalic acid, naphthalene-1 : 8-dicarboxylic acid, is prepared from acenaphthene by oxidation with sodium dichromate and sulphuric acid. This preparation establishes the chemical constitution of the acid, the two carboxyl groups occupying the 1 : 8- or *peri*-positions. *Peri*-substituted naphthalenes behave very much like *ortho*-substituted benzene derivatives. Naphthalic acid, for example, very readily forms the cyclic anhydride, *naphthalic anhydride* (*cf.* phthalic anhydride). Naphthalic anhydride when boiled in neutral solution with mercuric acetate undergoes




mercuration to yield a mercuri-anhydride, which with bromine is converted into 8-bromonaphthoic acid.¹ The latter is a useful compound for the synthesis of anthanthrones (*q.v.*).

2-Naphthoic acid and nitrile can be converted into the corresponding aldehydes. 2-Naphthoyl chloride undergoes reduction with hydrogen in the presence of a palladium catalyst to give 2-naphthaldehyde (*Rosenmund reaction*), and the nitrile gives the aldehyde when reduced by means of stannous chloride and hydrogen chloride (*Stephen method*). The latter method fails to take place with the 1-nitrile owing to steric hindrance, but the 1-aldehyde is prepared by a modification of Gattermann's synthesis with naphthalene, hydrogen cyanide, and aluminium chloride in chlorobenzene as solvent.²

Among other derivatives of naphthalene may be mentioned

acenaphthene, C_{10}H_6 , m.p. 95°, b.p. 277°, which is obtained from

¹ H. G. Rule and A. J. G. Barnett, *J.*, 1932, 176. F. C. Whitmore *et al.*, *J.A.C.S.*, 1929, 51, 1831, 3363. ² L. E. Hinkel, E. E. Ayling, and J. H. Benyon, *J.*, 1936, 340.

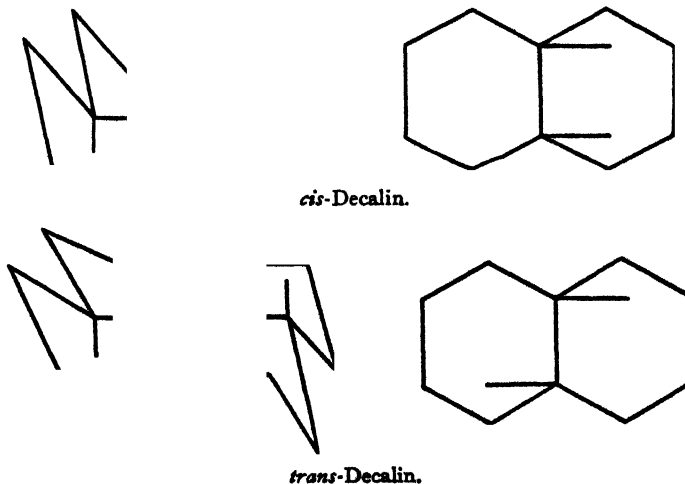
coal tar. On careful oxidation with sodium bichromate it is converted into acenaphthene-quinone, $C_{10}H_6$ , m.p. 261° , naphthalic acid being formed at the same time. Acenaphthene may be prepared synthetically by treating α -bromoethyl-naphthalene, $C_{10}H_7 \cdot CH_2 \cdot CH_2Br$, with alcoholic potash.

STRAINLESS RINGS AND CONDENSED RING STRUCTURES

For many years following the introduction of Baeyer's Strain Theory, ring structures were represented as being planar in configuration. Large rings containing seven or more ring atoms were supposed to be unstable and to exist in a condition of strain, due to the distortion of the valency bonds from the normal angle of 109° . From 1925 onwards these ideas were modified by the work of Ruzicka on stable large ring compounds such as muscone and civetone (p. 386), and by Hückel's investigations on the decalins and hydrindanes.

Fusion of Two Six-membered Rings.—The most important developments of the Sachse-Mohr theory of strainless rings have arisen from its application to saturated condensed ring systems. We have seen (p. 384) that cyclohexane can exist in two strainless conformations; the *chair* and the less stable *boat* conformation. The energy barrier separating the two forms is, however, so low that it is not surprising that their separation has not been effected by the methods which have proved so fruitful in other fields of stereochemistry.

Mohr, in 1918, was the first to suggest that two buckled cyclohexane rings could be condensed together either by *cis*- or by *trans*-linkages

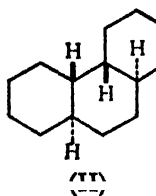
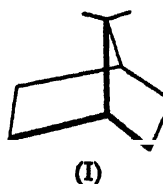


yielding decahydronaphthalenes (the decalins). The two decalins, however, should be stable, the two cyclohexane rings being locked or clamped to give "fixed" structures as shown in the formulæ, where

the positions of the hydrogen atoms attached to the two common carbon atoms are indicated by bonds. The *trans*-decalin is composed of two chair forms and the *cis*-decalin of two boat forms. Two decalins were in fact obtained (see below) and proof thus appeared to be provided that the cyclohexane ring can indeed exist in the chair and boat conformations. Electron diffraction experiments, however, have shown that although the Mohr picture of *trans*-decalin is correct, the *cis*-isomer likewise contains two *chair* forms and not two *boat* forms as had previously been imagined.¹ Both decalins therefore contain two chair forms, but differently arranged. The *cis*-decalin structure is shown in the annexed formula.



A survey of fully hydrogenated polycyclic compounds shows that generally the cyclohexane ring occurs in the preferred chair conformation. The boat conformation is found in certain cyclic compounds in which the molecule is locked by a 1 : 4-bridge or by being a member of a tri-cyclic system. This is exemplified by bicyclo-[1 : 2 : 2]-heptane (I) and by the perhydrophenanthrene (II). Models of the latter compound show it must contain at least one boat form.

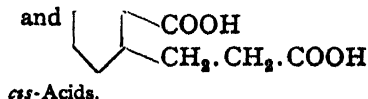
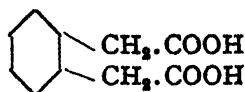
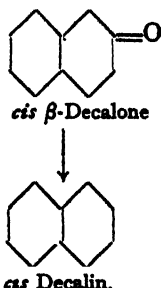
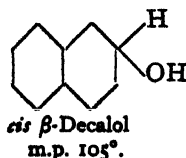


The existence of two decalins was established experimentally by Hückel, who started from the two known forms of β -decalol (decahydro- β -naphthol). These two compounds, m.p. 105° and 75° respectively, had been isolated by earlier workers from the reduction products of β -naphthol, although the nature of their isomerism was not known.

Hückel found that on oxidation with potassium dichromate and acetic acid each β -decalol gave rise to a different β -decalone, a fact which could be explained on Mohr's theory but not on the basis of a plane ring structure. Each decalone was reduced to a decalin by use of amalgamated

¹ O Hassel and H. Viervoll, *Acta Chem. Scand.*, 1947, 1, 149. O. Bastiansen and O. Hassel, *Nature*, 1946, 257, 764.

zinc and hydrochloric acid (*Clemmensen* method), and each decalol was converted by oxidation with cold acid permanganate solution into a mixture of cyclohexane-1:2-diacetic acid and cyclohexane-1-carboxy-2-propionic acid. These two acids as obtained from β -decalol, m.p. 105° , were of the *cis* configuration. This decalol and the related decalone and decalin are therefore also of *cis* structure.



The other series of compounds prepared from β -decalol, m.p. 75° , were proved in a similar manner to possess *trans* structures. The physical properties of the two decalins are given below : ¹

trans-Decalin : m.p. -31.47° , b.p. 185.5° , d_4^{20} 0.869, n_D^{20} 1.4701.

cis-Decalin : m.p. -43.26° , b.p. 194.6° , d_4^{20} 0.896, n_D^{20} 1.4811.

The same two decalins were also isolated by careful fractionation of the mixture obtained from the direct hydrogenation of naphthalene. They are stable compounds, although *cis* decalin is slowly and almost quantitatively isomerised into *trans* decalin at room temperature in contact with aluminium chloride, a reagent which is known to loosen the carbon bonds. The lower stability of the *cis* form under these conditions is in agreement with its somewhat greater heat of combustion.

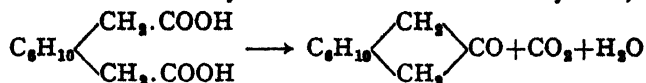
It may be noted that β -decalol has three asymmetric carbon atoms, an additional possibility of isomerism having been introduced owing to the *cis* and *trans* arrangement of the CHOH -group with respect to the decalin residue. All four of the expected racemic forms were isolated by Hückel, by reduction of the *cis* and *trans* β -decalones. Reduction of the oximes of the decalones resulted in the separation of four racemic β -amino-decalins.

Fusion of a Six- with a Five-membered Ring.—Theoretically a plane five-membered ring can only be attached to cyclohexane to form a strainless compound if the union is by *cis* linkages. On the assumption of buckled rings, however, the tension arising from *trans* coupling is not great.

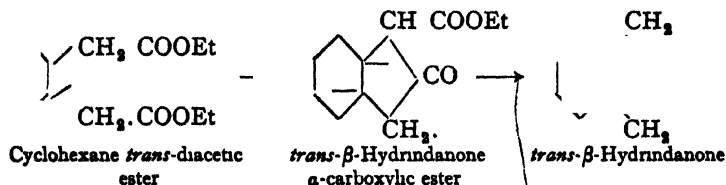
Hückel made a careful study of the hydrindane system and isolated both *cis* and *trans* hydrindanones. The structures of these

¹ W. F. Seyer and R. D. Walker, *J.A.C.S.*, 1938, 60, 2125.

compounds follow from their mode of formation from *cis* and *trans* cyclohexane-diacetic acids by distillation with acetic anhydride,



or from the corresponding esters by an internal acetoacetic ester condensation in the presence of sodium ethoxide, followed by hydrolysis with mineral acid and loss of carbon dioxide. Thus with the *trans* ester,



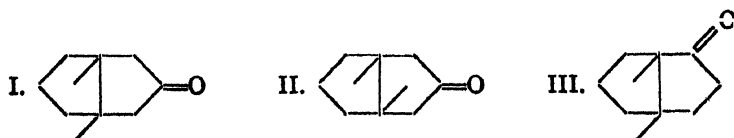
trans- β -Hydrindanone is more stable than the *cis*-compound and has a lower heat of combustion. This is not in agreement with theoretical conclusions, and led Hückel to suggest that the strain theory cannot be applied in a simple manner to a bicyclic system.

The above configurations were also confirmed by reducing the ketones to the hydrindanols ($\text{CO} \longrightarrow \text{CHOH}$). As was to be expected from the models, *cis* β -hydrindanol occurs in two geometrical isomerides, each of which possesses a plane of symmetry containing the H and OH groups.



Only one *trans*- β -hydrindanol exists and this is a racemic compound which can be resolved into two optically active forms.

Fusion of Two Five-membered Rings.—Theoretical considerations suggest that any deviation from the plane model in either 5-ring will result in tension and that only fusion in the *cis* position will give a stable compound. This is borne out by the work of Linstead, Meade and Cook ¹



on the bicyclo-octanones. These compounds were prepared from the *cis* and *trans* cyclopentane-diacetic acids, $\text{C}_5\text{H}_8(\text{CH}_2\text{.COOH})_2$. Of the *cis* and *trans* β -bicyclo-octanones (I and II), the former is the more readily obtained and is the more stable. *cis* α -Bicyclo-octanone (III) was the only α -ketone which could be isolated, as the *trans* isomeride is apparently converted into the *cis* form under the influence of heat.

Similar stability relationships exist among anhydrides of this type. Thus the anhydride of *cis* cyclopentane-1-carboxy-2-acetic acid is more stable than that of the *trans* compound.¹

¹ R. P. Linstead and E. M. Meade, *J.*, 1934, 935; A. H. Cook and Linstead, *ibid.*, 946.

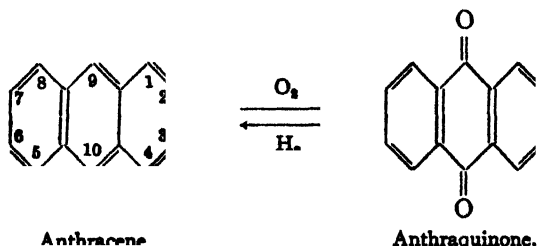
XVI

Anthracene Group

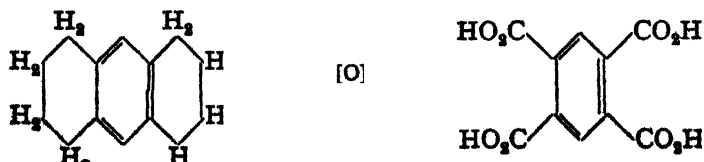
Anthracene, $C_{14}H_{10}$, is the parent substance of a number of interesting compounds and valuable dye-stuffs. It is present to the extent of 0.25 to 1.1 per cent. in coal tar, and distils over in the anthracene oil, boiling above 270° . In this it is mixed with various products such as phenanthrene, chrysene, carbazole and paraffins, which are difficult to remove. Crude anthracene crystallises out from the mixture on cooling and is separated in filter presses. The product, which contains about 30 to 50 per cent. of anthracene, is purified by treatment with pyridine bases or furfural, when most of the phenanthrene, fluorene and other impurities pass into solution, leaving an 80 to 90 per cent. anthracene. The latter is obtained in finely-divided form by sublimation or distillation in steam, and if required for the preparation of dyes is then worked up directly into anthraquinone.

Anthracene may be further purified by means of the Diels-Alder reaction (p. 593). It crystallises in colourless plates having a blue fluorescence when pure and a yellow fluorescence when impure; and with picric acid it forms an addition compound, $C_{14}H_{10}$, $C_6H_2(NO_2)_3OH$, crystallising in red needles, m.p. 138° .

Constitution and Synthesis of Anthracene.—The constitution of anthracene follows from the synthesis of the hydrocarbon and of its oxidation product, anthraquinone, into which it is easily converted and from which it is readily obtained by reduction. Anthracene is a linear

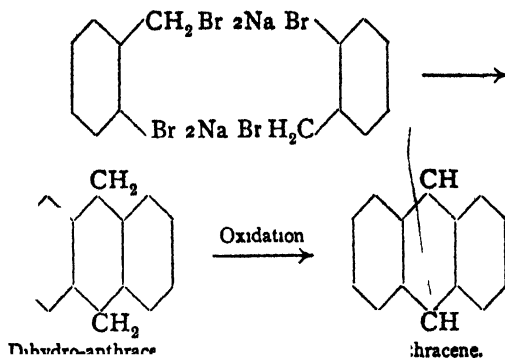


molecule consisting of three condensed benzene rings (Graebe and Liebermann) and this is confirmed by its reduction to 1:2:3:4:5:6:7:8-octahydroanthracene which undergoes oxidation to give benzene-1:2:4:5-tetracarboxylic acid.

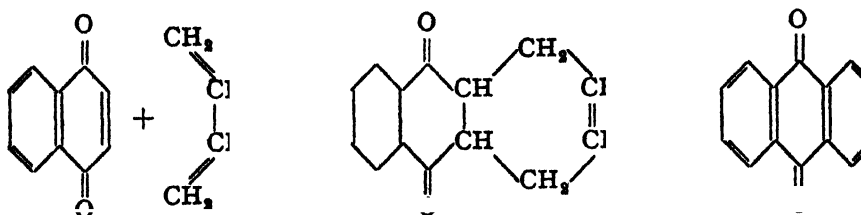


Anthracene is formed when *o*-bromobenzyl bromide is treated with sodium. In this reaction the first product is dihydro-anthracene, which is readily converted into anthracene by oxidation.

A number of other syntheses of anthracene have also been effected. Synthetic methods of preparing anthraquinone, and the formation of anthracene from this compound and from alizarin, are described later.



The Diels and Alder synthesis of anthraquinone may, however, be given here as it throws light on the constitution of the quinone and of anthracene into which it is converted by distillation with zinc dust. α -Naphthaquinone and butadiene are heated together in alcoholic solution at 100° . The resulting tetrahydroanthraquinone is readily oxidised by chromic acid to anthraquinone.



Fine Structure of Anthracene.—Anthracene is a resonance hybrid with structures such as I and II as the main contributing forms.

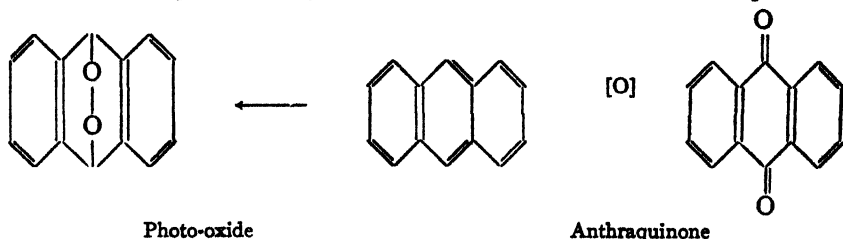


According to the Fries rule structures such as I will be more stable than II, since they contain only one quinonoid ring whereas II contain two such rings. The chemical properties of anthracene, represented by structure I.¹

¹ See further evidence by Fieser and Lothrop, *J.A.C.S.*, 1936, 58, 7.

Properties of Anthracene.—Anthracene is characterised by the great reactivity of the 9 : 10- or *meso*-positions. For example, reduction with sodium and alcohol results in the addition of two hydrogen atoms to the "middle group," with the formation of 9:10-*dihydroanthracene*. Further hydrogenation by different methods yields 1:2:3:4-*tetrahydroanthracene*, 1:2:3:4:5:6:7:8-*octahydroanthracene*, and *perhydroanthracene*, $C_{14}H_{24}$, the fully hydrogenated compound.¹ Three forms of the latter compound are known.

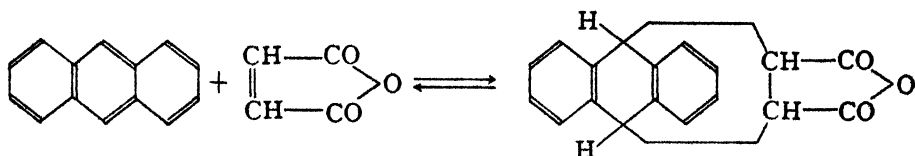
Oxidation of anthracene also occurs at the *meso*-positions and two types of product may be obtained. Oxidation with chromic anhydride in acetic acid solution gives an excellent yield of anthraquinone. On the other hand *photo-oxidation* can be effected by a combination of light and air to give a photo-oxide in which a 1 : 4-peroxide bridge stretches across the middle ring.² This photo-oxide liberates iodine from potassium



iodide, is reduced by hydrogen to 9 : 10-dihydroxy-9 : 10-dihydroanthracene, and with hydrochloric acid gives chloranthrone.

Bromination of anthracene gives the 9 : 10-dibromide.

The reactivity of the *meso*-positions is also clearly shown by the ability of anthracene to react as the diene component in the Diels-Alder reaction. When heated with maleic anhydride in boiling xylene solution, anthracene yields a crystalline product, anthracene-maleic acid.



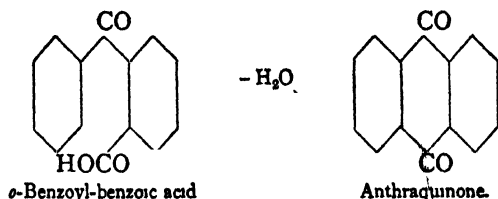
Advantage may be taken of this reaction to purify anthracene since the product may be separated from contaminating hydrocarbons such as phenanthrene and converted back to the anthracene by heating *in vacuo*.

Many substituted anthracenes are obtained from the corresponding anthraquinones.

Anthraquinone is obtained synthetically when *o*-benzoyl-benzoic acid is heated with phosphorus pentoxide or sulphuric acid. This acid can be prepared by heating phthalic anhydride with benzene and aluminium chloride.

¹ J. W. Cook, N. A. McGinnis and S. Mitchell, *J.*, 1944, 286. ² C. Dufraisse and M. Gerard *Bull. Chim. Soc.*, 1937, 4, 2052. W. Bergmann and M. J. McLean, *Chem. Reviews*, 1941, 28, 367.

Anthraquinone is manufactured in America chiefly by this process, but in this country it is prepared industrially in large quantities for the preparation of alizarin and *meso*-benzanthrone by oxidising 90 per cent. anthracene with sodium bichromate and sulphuric acid. The product so obtained may be freed from impurities derived from the phenanthrene, fluorene, etc., present in crude anthracene, by dissolving it in hot concentrated sulphuric acid, in which anthraquinone dissolves unchanged

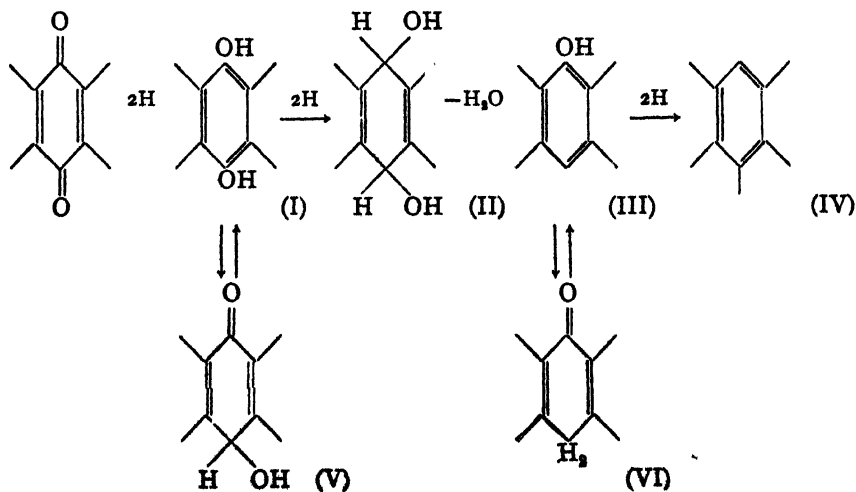


while the original impurities or their oxidation products are converted into water-soluble sulphonic acids. Hence, on diluting the acid solution with water, only anthraquinone is precipitated. It may be further purified by distillation in steam or by treatment with pyridine.

The Diels-Alder synthesis of anthraquinone has already been mentioned (p. 592).

Anthraquinone melts at 285° , boils at 382° , and crystallises in colourless needles or prisms which readily sublime. It is a very stable compound, and is only attacked with difficulty by nitric acid and oxidising agents. In its whole behaviour it stands much closer to the diketones than to the quinones, possessing neither the characteristic pungent smell of quinone nor its property of being reduced to hydroquinone with sulphurous acid. With hydroxylamine it yields bright yellow needles of *anthraquinone oxime*, which decompose at 224° .

Depending on the agents used anthraquinone on reduction yields a number of products, some of which are tautomeric substances. On



reduction in alcoholic suspension with alkaline sodium hydrosulphite, $\text{Na}_2\text{S}_2\text{O}_4$, or by warming with zinc dust and alkali, anthraquinone is converted into anthraquinol (I), which is tautomeric with oxanthrone (V). Both forms may be isolated according to the experimental conditions. Anthraquinol is an unstable substance which gives a beautiful and striking reaction used as a test for anthraquinone. The greenish-yellow compound dissolves in alkali, giving a blood-red colour; when shaken with air, however, the red solution is very rapidly decolorised and yellow anthraquinone separates. The alkaline solution contains a considerable amount of hydrogen peroxide.

More vigorous reduction of anthraquinone with tin and hydrochloric acid yields anthrone (VI), through the dihydroxy-compound (II). Anthrone when dissolved in warm alkali and precipitated by acids is converted into the tautomeric form, anthranol (III). The keto form is more stable than the enolic form. This is somewhat surprising in view of the known stability of the phenols and the instability of their ketonic forms. The two tautomers are readily differentiated, since anthrone in solution is non-fluorescent under ultra-violet light, whereas anthranol exhibits a blue fluorescence. From either compound in organic solvents an equilibrium mixture containing a large proportion of anthrone is obtained.

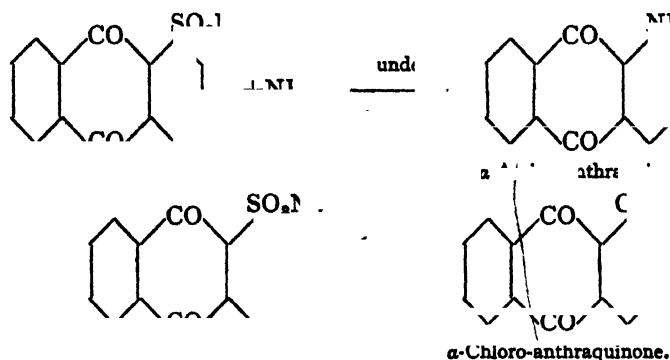
Finally, by reducing anthraquinone with zinc dust and aqueous ammonia anthracene (IV) is obtained.

Anthraquinone Sulphonic Acids

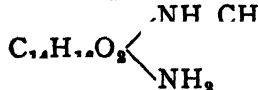
The sulphonation of anthraquinone provides a striking illustration of the manner in which the course of a reaction may at times be influenced by the addition of an apparently indifferent substance (compare p. 533, on the conversion of naphthalene into phthalic acid). Sulphonation in the ordinary way only yields β -sulphonic acids, together with an exceedingly small quantity of α -acids. On the other hand, it was shown independently by Iljinsky and R. E. Schmidt that the presence of a small amount of mercury so favours the formation of α -sulphonic acids that the product of reaction is almost pure α -acid. This action of mercury practically brings about a complete displacement of the normal position of substitution, and also enables the reaction to be carried through much more easily. It is therefore of great value industrially since anthraquinone sulphonic acids are important intermediates in the preparation of dye-stuffs. So far as has been observed, however, this effect is peculiar to anthraquinone derivatives.

Another method of preparing α -anthraquinone sulphonic acids is to heat α -nitro-anthraquinones with aqueous solutions of neutral alkali sulphites, when the nitro-group is readily exchanged for the sulphonic group. Thus α -nitro-anthraquinone yields anthraquinone α -sulphonic acid, and the 1:5- and 1:8-dinitro-derivatives give the corresponding 1:5- and 1:8-disulphonic acids.

The acid group in the sulphonic acids is comparatively easily removed. For example, the sodium salt of anthraquinone α -sulphonic acid gives α -amino-anthraquinone with ammonia under pressure and α -chloro-anthraquinone with chlorine. The β -amino- and chloro-anthraquinones can be prepared similarly but less readily. Reduction with zinc



ammonia converts anthraquinone- α -monosulphonic acid into *anthracene α -sulphonic acid*, which on fusion with alkali gives *α -anthrol*. The nitration of anthraquinone α -sulphonic acid leads to the formation of two **nitro-anthraquinone sulphonic acids**, with the substituents in the 1:5- and 1:8- positions respectively. These are readily reduced to 1:5- and 1:8- **amino-anthraquinone sulphonic acids**, which can be diazotised and coupled with phenols and amines. When heated with methylamine these amino-acids exchange the sulphonic group for the residue —NH.CH_3 , with the production of 1:5- and 1:8-*monomethyl-diamino-anthraquinones*.



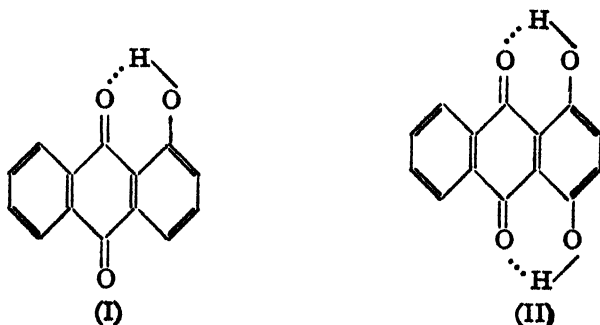
It is obvious that a great number of anthraquinone derivatives can be prepared by such methods.

Hydroxy-anthraquinones

Hydroxy-anthraquinones can also be prepared from chloro- and bromo-anthraquinones by fusion with alkali, and further by the anthraquinone synthesis mentioned on p. 592, using phenols in place of benzene, *i.e.*, by heating phthalic anhydride with mono- or dihydric phenols in the presence of aluminium chloride. A reaction of practical value is the formation of polyhydroxy-anthraquinones by oxidising anthraquinone or its simple hydroxy derivatives by means of hot fuming sulphuric acid, see p. 600. The addition of a little boric acid considerably increases the yield.

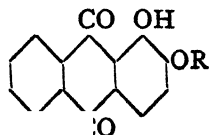
The properties of the hydroxy-anthraquinones are discussed in the sequel, but in view of the importance of the anthraquinone dye-stuffs with hydroxyl groups in the 1-position it is important to realise that such compounds contain intramolecular hydrogen bonds. This was

conclusively established by the infra-red absorption of anthraquinone, 1-hydroxy-anthraquinone (I), and 1:4-dihydroxy-anthraquinone (II).¹ Anthraquinone shows the usual carbonyl absorption band at 1675 cm.^{-1} .



The monohydroxy-anthraquinone (I) shows two bands: the normal carbonyl band at 1675 cm.^{-1} , and another at 1635 cm.^{-1} due to the carbonyl group participating in the hydrogen bonding. Only the latter band appears in the dihydroxy-anthraquinone (II) since both carbonyl groups are involved in the hydrogen bonding.

Alizarin, 1:2-dihydroxy-anthraquinone is the most important hydroxy derivative. It ranks with indigo as the most valuable of all dye-stuffs, whether synthetic or natural. Prior to 1869 it was exclusively prepared from *Madder* (*Rubia tinctorum*), a shrub growing to about three feet

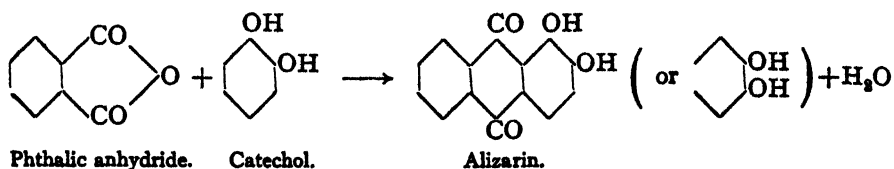


in height, which was cultivated in France. It contains in its root a number of glycosides such as *ruberythric acid*, *rubianic acid* and *rubian*. *Ruberythric acid* is an alizarin derivative of the annexed formula,² where R is a residue of the disaccharide primverose (a D-xylosido-D-glucose). On hydrolysis with hot dilute sulphuric acid it yields alizarin, D-xylose and D-glucose. *Rubianic acid*, on the other hand, is hydrolysed to purpurin (1:2:4-trihydroxy-anthraquinone) and carbohydrate(s).

Constitution of Alizarin.—In 1865 Graebe and Liebermann obtained the hydrocarbon anthracene by distilling natural alizarin with zinc dust. This fact, together with the discovery of the method described below of preparing alizarin artificially, pointed to the compound being an anthraquinone derivative in which two hydrogen atoms were replaced by two hydroxyl groups. The formation of phthalic acid by the oxidation of alizarin proved that both hydroxyl groups were contained in the same

¹ M. St C. Flett, *J.*, 1948, 1441. ² Jones and Robertson, *J.*, 1933, 1167; D. Richter, *ibid.*, 1936, 1701.

benzene nucleus, and the synthesis of alizarin (accompanied by *hystazarin*, now known to be 2 : 3-dihydroxy-anthraquinone) from phthalic anhydride and catechol showed them to be in the *o*-position to one another.

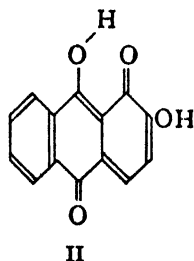
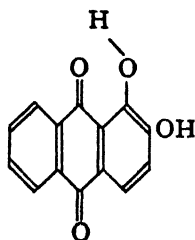


Finally, the existence of two isomeric nitro-alizarins having the nitro-group in the same benzene nucleus as the hydroxyl groups is a proof that the hydroxyl groups occupy the 1 : 2- and not the 2 : 3-positions.

It has already been emphasised that the formation of insoluble lakes with metallic mordants is of the highest importance for the practical utilisation of hydroxy-anthraquinones in wool dyeing and cotton printing.

Liebermann and Kostanecki showed that the presence of one hydroxyl group in the above compounds does not confer the property of forming coloured lakes in sufficiently high degree to give a good dye. For this purpose it is necessary to have two hydroxyl groups which must stand in the ortho- or "alizarin" position to one another. Other positions of the hydroxyls either fail to give strong dyeing properties or lead only to improvement with respect to a few special mordants.

It will be noted that the alizarin dye-stuffs are resonance hybrids with contributing structures such as I and II.



Technical Preparation of Alizarin.—Graebe and Liebermann were the first to prepare alizarin artificially, thus producing for the first time in a laboratory a natural vegetable colouring compound. They obtained it by fusing dibromo-anthraquinone with potassium hydroxide, a method not adapted to large scale practice. The industrial preparation was only established successfully when W. H. Perkin in England and Caro, Graebe and Liebermann in Germany simultaneously—the patent applications were filed on succeeding days, 28th and 29th June 1869—substituted the cheaper anthraquinone sulphonic acids for the expensive dibromo-anthraquinone. It was at first believed that the sulphonation of anthraquinone led to the formation of a disulphonic acid, which then yielded alizarin on fusion with alkali. Perkin, however, proved that the essential product was the

β -monosulphonic acid, so that the additional hydroxyl group introduced into the adjacent α -position during the fusion must be the result of aerial oxidation. Four years later, in 1873, Koch obtained an increased yield of alizarin by adding the calculated amount of an oxidising agent (sodium nitrate or chlorate) to the melt, which is the manner in which the technical preparation is still conducted.

The artificial preparation of alizarin was the first synthesis of a valuable natural dye-stuff to be successfully carried out on the industrial scale. Synthetic alizarin soon completely displaced the natural product from the market, and led to the decay of madder cultivation in the Mediterranean countries. Thus France with a yearly production of about 70,000 tons of madder lost a valuable commercial article.

Properties and Use of Alizarin.—In the pure state alizarin crystallises in beautiful red prisms or needles, melting at 289° . It dissolves sparingly in water, but is readily soluble in alkali. Alizarin yields insoluble coloured "lakes" with mordants; with aluminium and tin oxides the colour is red, with chromium oxide a brownish violet and with ferric oxide a violet black. It is by the aid of these mordants that the alizarin is attached to the fabric, and the lakes, of which aluminium red is the most important, therefore constitute the actual dye-stuffs.

Alizarin and the closely related compounds purpurin, anthrapurpurin and flavopurpurin are typical mordant dyes. They dye both wool and cotton with the aid of mordants, giving colours which are very fast to light and washing. Consequently they are of great value commercially.

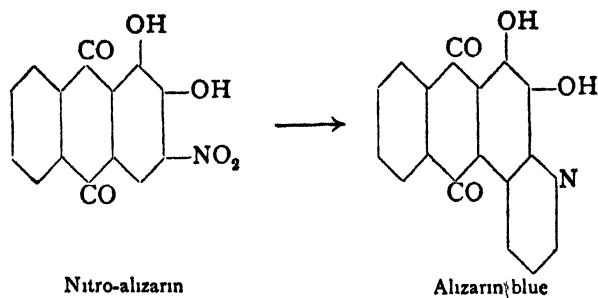
One of the best-known alizarin colours is the fiery **Turkey Red** which is very fast to washing, acids and light. The cotton fabric or yarn to be dyed is steeped in an aqueous solution of **Turkey Red** oil and dried. It is then mordanted with aluminium acetate, dried and dyed in an alizarin bath containing **Turkey Red** oil and a little chalk. Finally, the material is steamed under pressure and the colour cleared by washing with soap. The same complex colour lake may be prepared directly by prolonged heating of alizarin, aluminium acetate and calcium acetate in water, and has been shown to contain alizarin, Al and Ca in the proportions 4 : 2 : 3. Five molecules of water are also present, which are essential parts of the structure. No fatty acid is contained in the dye, the only function of the **Turkey Red** oil used in the dyeing process being apparently to fix the metallic oxides as soaps on the fibre and to deposit the lake in a very finely dispersed state.¹ It is this almost colloidal condition of the dye which is believed to be responsible for the brilliant colour. Calcium may be replaced by certain other divalent metals, e.g. tin, and aluminium by trivalent iron.

Turkey Red oil is made by treating castor oil with sulphuric acid and then neutralising the liquid.

Alizarin gives valuable products on nitration. The resulting *nitro-alizarin* is mainly the β -compound, and is used under the name

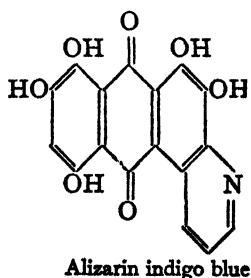
¹ H. E. Fierz-David and M. Rutishauser, *Helv. Chim. Acta*, 1940, 23, 1298.

of alizarin orange. With alumina as mordant it dyes an orange colour. When a mixture of β -nitro- and β -amino-alizarin is heated with glycerol and sulphuric acid (*cf.* quinoline synthesis) it yields alizarin blue, which may be used as a substitute for indigo blue in wool and cotton dyeing. Alizarin blue bears the same structural relationship to



alizarin as quinoline does to benzene. Alizarin blue was first made by Prud'homme in 1877 and its structure was determined a few years later by Carl Graebe. The synthesis is clearly a forerunner of the Skraup reaction and undoubtedly suggested to Skraup its synthetic possibilities.

One of the great advances in the anthraquinone dye-stuffs field was the discovery by Bohn in 1888 that hydroxyl groups can be introduced into the anthraquinone molecule by means of fuming sulphuric acid. The discovery was made with alizarin blue which yielded several new



dye-stuffs in this way. For instance, with 80 per cent. fuming sulphuric acid at room temperature, it yields alizarin indigo blue (see annexed formula), three hydroxyl groups having been introduced into the molecule. The reaction was discovered independently by R. E. Schmidt, who also made the important observations that the reaction is catalysed by traces of mercury, selenium, etc., and that it can be controlled by the addition of boric acid.

Quinizarin, 1:4-dihydroxy-anthraquinone, may be obtained by oxidising anthraquinone with fuming sulphuric acid in the presence of boric acid or from phthalic anhydride and *p*-chlorophenol in the presence of sulphuric acid and boric acid.¹

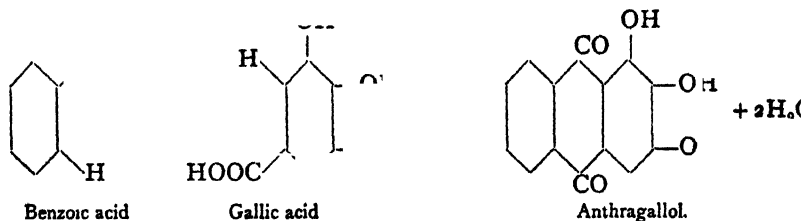
¹ L. A. Bigelow and H. H. Reynolds, *Organic Syntheses*, 4, 78.

Anthrarufin, 1:5-dihydroxy-anthraquinone, is prepared by heating anthraquinone-1:5-disulphonic acid (see p. 595) with milk of lime at 200°. It is used in the manufacture of *Alizarin Saphirol B*.

Trihydroxy-anthraquinones, $C_{14}H_8O_3(OH)_3$

Some of these compounds are also valuable mordant dyes.

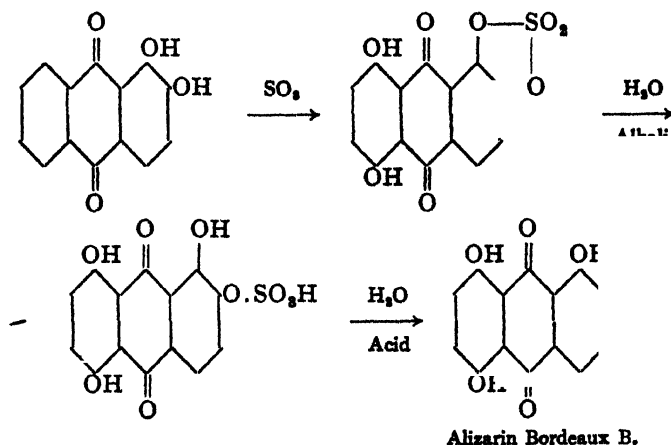
Anthragallol, 1:2:3-trihydroxy-anthraquinone, is prepared by heating equimolecular amounts of benzoic acid and gallic acid with con-



It forms brown lakes with chromium mordants and is used under the name of "alizarin brown" or "anthracene brown."

Polyhydroxy-anthraquinones

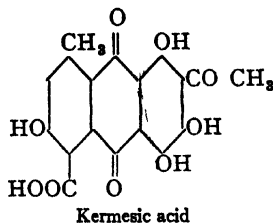
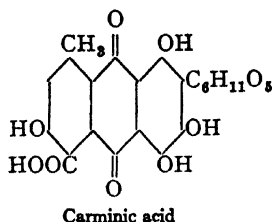
Polyhydroxy-anthraquinones are of technical interest and are prepared by the oxidation of hydroxy-anthraquinones with fuming sulphuric acid. The *Bohn-Schmidt process* (p. 600) is illustrated by the formation of **Alizarin Bordeaux B(By)** from alizarin.



In the presence of boric acid intermediate hydroxy-compounds can be isolated. For example, in the above reaction fuming sulphuric acid and boric acid give **Brilliant Alizarin Bordeaux R**, 1:2:5-trihydroxy-anthraquinone. **Alizarin cyanine**, 1:2:4:5:8-pentahydroxy-anthraquinone, $C_{14}H_8O_3(OH)_5$ is obtained by oxidising alizarin bordeaux with manganese

dioxide and sulphuric acid. It gives a purple shade of blue with chromium mordant. **Rufigallic acid**, 1 : 2 : 3 : 5 : 6 : 7-*hexahydroxy-anthraquinone*, is produced from gallic acid by heating with concentrated sulphuric acid, when 2 mols. of the gallic acid condense with one another (*cf.* anthragalol). It colours a chromium-mordanted fabric brown.

Other polyhydroxyanthraquinones are carminic acid and kermesic acid. **Carminic acid**, one of the fastest mordant dyes known, is the colouring matter of cochineal, obtained from the dried bodies of cochineal insects (*Coccus cacti*). It has the following structure, though the nature of the long side-chain is not known.



Kermesic acid (from *Coccus ilicis*) is no longer used.

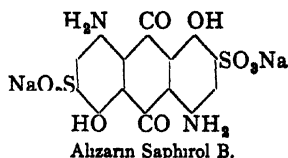
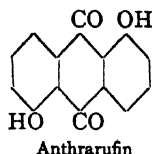
DYE-STUFFS OF THE ANTHRAQUINONE GROUP¹

Under this heading are included many valuable dye-stuffs, which may be divided into three main types.

(a) *Mordant dyes* such as **alizarin**, **purpurin** and other polyhydroxy anthraquinones already described in the foregoing pages.

(b) *Acid dyes*, which in the form of their sodium salts are absorbed directly on wool to give fast and bright colours. They have very little affinity for cotton even if mordants are used and they form no lakes with tannin. Examples of this kind are the following sulphonated amino-anthraquinones.

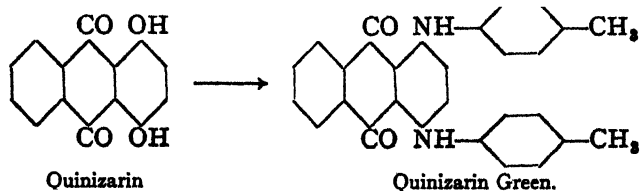
Alizarin Saphirol B was the first of this group to be discovered (R. E. Schmidt, 1897). It is prepared from anthrarufin by sulphonating it to



the 2:6-disulphonic acid, followed by nitration in the 4:8-positions and final reduction to the diamino-compound. The sodium salt of the resulting product is Alizarin Saphirol B. It dyes wool a fast blue colour.

¹ See *The Synthetic Dyestuffs and Intermediate Products*, by Cain and Thorpe, revised by Thorpe and Linstead (Griffin & Co., 1933). *The Chemistry of Synthetic Dyes*, by K. Venkataraman (Academic Press, Inc., 1952).

Alizarin Cyanine Green (By).—Negative groups in the α -positions in anthraquinone are relatively labile and when quinizarin, its leuco-compound or 1:4-dichloro-anthraquinone is heated with *p*-toluidine the α -substituents are displaced by *p*-toluidine residues to form Quinizarin



Green. The latter is then disulphonated, when one sulphonic group enters into a position ortho to NH in each toluidine nucleus. The sodium salt of this acid is Alizarin Cyanine Green (By), an acid dye for wool and silk, although it is generally applied with a mordant to give a faster colour.

Another similar dye-stuff is **Alizarin Pure Blue B**, which is 1-amino-2-bromo-anthraquinone having a sulphonated *p*-toluidine residue attached to position 4.

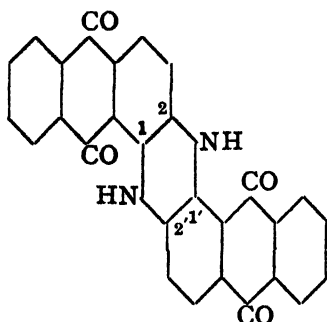
Amino-anthraquinones and their derivatives have been found to be valuable dyes for use with *cellulose acetate silk*, which is not dyed satisfactorily by the majority of the dye-stuffs employed for other textiles.

(c) *Vat dyes*, which are applied chiefly to cotton, include many simple and complex derivatives of anthraquinone, a few examples of which are described in this section.

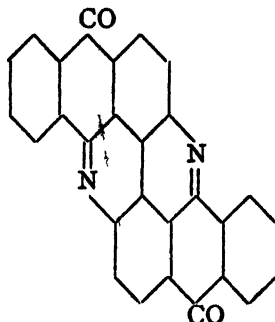
A vat dye functions by means of two properties: the ability of the insoluble dye-stuff to form a soluble salt on reduction by means of an alkaline reducing agent, and the ability of this sodium salt to combine with the fibre. When anthraquinone is treated with reducing agents such as sodium hydrosulphite it yields the *leuco compound*, anthraquinol, in the form of its disodium salt (p. 595), which rapidly oxidises back to anthraquinone in air. The leuco compound, however, possesses little affinity for the fibre and is of no use in dyeing. In contrast, R. E. Schmidt found that the aroyl derivatives of aminoanthraquinones possess strong colours and yield reduction products (leuco compounds) which are absorbed by (*i.e.* are substantive to) cotton. A simple example of this type of vat dye-stuff is 1-benzamido-anthraquinone (**Algol Yellow WG**) which, however, is no longer used. A dye-stuff which is very fast to light is 1:4-dibenzamido-anthraquinone (**Indanthrene Red 5GK**). All dye-stuffs of this class contain at least one α -aroylamino group.

Indanthrone, Indanthrene Blue.—Until the end of last century the only vat dye-stuffs were indigo and Tyrian Purple. In 1901 Rene Bohn prepared Indanthrene Blue R, the first anthraquinone vat dye. Bohn had carried out research under Heumann and attempted to extend Heumann's indigo synthesis to the amino-anthraquinone series. Accordingly he heated 2-aminoanthraquinone with chloracetic acid and caustic soda. The product, however, proved to be not the anthraquinone

derivative of indigo, but the substance formed by a condensation of two molecules of the aminoanthraquinone. The dye-stuff now generally termed **Indanthrone** is prepared commercially by fusing 2-aminoanthraquinone with potassium hydroxide at 200° to 300° . The potassium salt of a blue hydro-compound is obtained, which on being dissolved in water in the presence of air deposits the blue dye indanthrone. This dye-stuff is remarkable for the beauty and permanence of the blue shades it produces. From its mode of formation and general behaviour it is assigned the following constitution (R. Scholl, 1903), according to which it is regarded as a derivative of dihydro-phenazine (described later):



Indanthrone



Flavanthrone

This structure is proved by the synthesis of indanthrone by the condensation of two molecules of 1-chloro-2-amino-anthraquinone in boiling nitrobenzene with sodium carbonate and powdered copper as condensing agent. Indanthrone is exceedingly stable. Owing to its insolubility it cannot be attached directly to the fibre, but with alkaline hydrosulphite solution it yields a blue reduction product, which is soluble in alkali and extremely sensitive towards atmospheric oxygen. In this form it is brought on to the fabric. It resembles indigo in being a blue *vat dye*, and is the first genuine vat dye of the anthracene series. The bath, however, is so strongly alkaline that it cannot be used for dyeing wool, but only for cotton. A number of halogen substitution products and other derivatives of indanthrone (*e.g.* algol blue 3 G, algol green G) are also used extensively as vat dyes.

By conducting the fusion of β -amino-anthraquinone with alkali at the very high temperature of 330° to 350° , dissolving the melt in water in the presence of air and filtering off the alkali-soluble by-products of the reaction, there is formed in place of indanthrone a yellow dye-stuff known as **flavanthrone** or **indanthrene yellow G**. In the modern technical method 2-aminoanthraquinone is boiled in nitrobenzene with antimony pentachloride.

Solubilised Indanthrone.—Indanthrone has to be employed from a strongly alkaline vat, rendering it unsuitable for application to woollen goods, which shrink in contact with alkali. The dye can be adapted for wool and silk by *solubilisation*. Soon after the introduction of the indigosol

process (see later), it was discovered by Scottish Dyes, Ltd., that anthraquinone dyes could be converted directly into soluble leuco-esters. For this purpose indanthrone is heated with oleum or chlorosulphonic ester, with the addition of a reducing metal such as zinc, copper or iron, and in the presence of a tertiary base, usually pyridine. The sodium salt of the resulting sulphuric ester is **Solubilised Indanthrene Blue**. In this product two of the keto groups in one anthraquinone residue have been reduced to the leuco state and esterified with sulphuric acid ($\text{CO} \longrightarrow \text{C.OH} \longrightarrow \text{C.O.SO}_3\text{Na}$). The other anthraquinone residue is not changed. Solubilised indanthrone is stable in neutral (or alkaline) solution and is absorbed readily by wool, silk and cotton. The dyed material is finally treated with nitrous acid or an acid bichromate solution, which hydrolyses off the sulphuric ester groups and oxidises the resulting leuco-compound back to indanthrone, which is thus firmly embedded in the fibre.

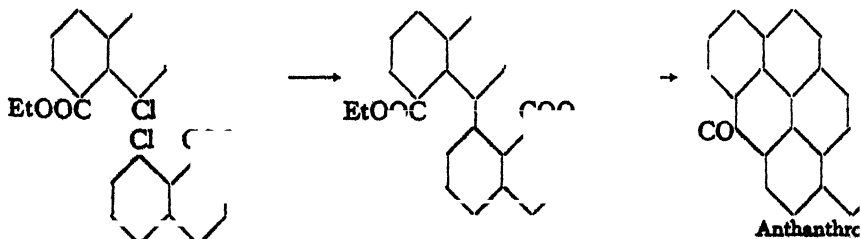
Complex Carbocyclic Quinones¹

Closely related to anthraquinone are a number of polycyclic quinones, which differ from anthraquinone itself in being highly coloured and in giving reduction products readily absorbed by the fibre. Compounds of this kind which function as vat dyes contain at least two carbonyl groups linked by a conjugated chain of alternate single and double bonds, and include in their molecular structure the characteristic systems of



pyrene or perylene. Examples of this type are found in anthanthrone and benzanthanthrone.

Anthanthrone is an orange red compound which does not melt below 300° . It was first prepared by Kalb in 1913 from 8-chloro-1-naphthoic ester. This when heated with copper bronze (*Ullmann reaction*) converted into 1:1'-dinaphthyl-8:8'-dicarboxylic ester, which on being warmed with concentrated sulphuric acid is cyclised to anthanthrone. Much better yields, however, are obtained by use of 8-bromo-naphthoic ester² (see p. 586). The cyclisation occurs in two stages, one ester group



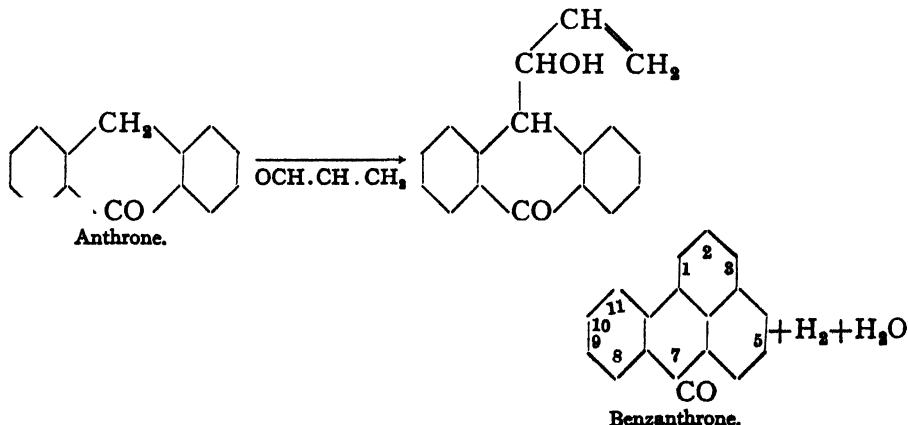
¹ See *The Synthetic Dyestuffs*, by Cain and Thorpe (Griffin, 1933).

² Rule, Pursell :

being first hydrolysed to a free carboxyl and rapidly forming a new ketonic ring by condensation with the neighbouring ring. The second ester group reacts somewhat more slowly.¹ The half way product having one ketonic ring gives a deep red solution in sulphuric acid owing to the formation of an oxonium salt, and the completion of the reaction is marked by a colour change to green as the second ring is produced to give the diketo compound anthanthrone. Cyclisation may also be effected by converting the ester groups in the dicarboxylic ester into acid chloride groups, followed by treatment with aluminium chloride.

Anthanthrone only dyes a weak yellow, and it is therefore employed as a dyestuff in the form of the more strongly coloured halogen derivatives, *e.g.* dichloro-anthanthrone (Indanthrene² Brilliant Orange) and dibromo-anthanthrone (Caledon Brilliant Orange, 4 RS). Halogen may be introduced directly into anthanthrone, or at the intermediate stage. The compounds give violet vats.

Benzanthrone Colours are prepared from *bensanthrone*, a yellow crystalline compound, m.p. 171°, which is itself of no value as a dye-stuff. Benzanthrone was discovered in 1905 by Bally, who obtained it as a result of heating glycerol and sulphuric acid with anthraquinone. It is now more usual to add copper powder prior to the introduction of glycerol, to effect the reduction of the quinone to anthrone, which is an intermediate in the reaction. The explanation advanced by Bally and Scholl³ assumes the reduction of some anthraquinone to anthrone, followed by condensation of the latter with acrolein (produced by dehydration of glycerol) to form an aldol, in accordance with the following scheme.



Substituents in the benzanthrone molecule are best indicated by the numbering system shown in the formula. Benzanthrone dissolves in sulphuric acid giving a deep red solution with strong yellow fluorescence.

¹ Rule and Smith, *J.*, 1937, 1009.

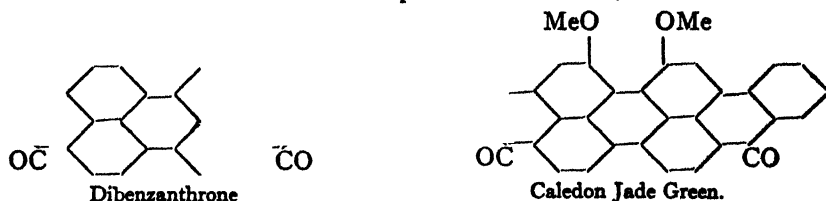
² "Indanthrene" is used as a trade name for the

fastest dyes produced by the German I. G. combine, and covers a wide variety of chemical types.

³ *Ber.*, 1911, 44, 1656. This mechanism appears to be supported by the work of F. G. Badder, and F. L. Warren, *J.*, 1938, 401. See also Meerwein, *J. pr. Ch.*, 1918 (2), 97, 284.

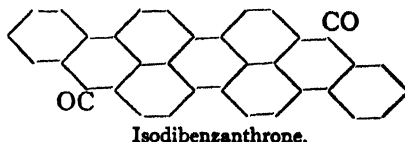
A deep blue vat dye is prepared from benzanthrone by fusion with alkali at $240-250^{\circ}$, when two molecules link together at the 3 and 4 positions with loss of hydrogen to form dibenzanthrone (Violanthrone, Indanthrene Dark Blue, B.O.).

A valuable derivative of dibenzanthrone is the dimethoxy compound known as **Caledon Jade Green**, a fine and very fast pale bluish-green colour. This can be prepared by oxidising dibenzanthrone with manganese dioxide and concentrated sulphuric acid at 0° , which introduces



two hydroxyl groups into the desired positions, followed by methylation in hot nitrobenzene solution with dimethyl sulphate and sodium carbonate. Or benzanthrone can be oxidised to 2-hydroxy-benzanthrone, using the same reagents, and this methylated to give the methoxy compound. Final mild treatment with potassium hydroxide and alcohol at 180° then yields Caledon Jade Green.

If benzanthrone is first halogenated in the 3-position and the resulting compound heated with alcoholic potash, condensation occurs with loss of two molecules of hydrogen halide to form **isodibenzanthrone (Isoviolanthrone)**, which dyes a more purple colour than its isomeride dibenzanthrone.

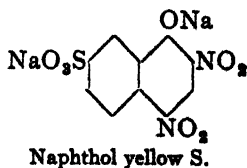


Classification of Dye-stuffs

The simplest method of classifying dye-stuffs is to arrange them according to the manner in which they are applied to the material. Representatives of all the more important types of dyes have already been described in earlier pages of this book and their characteristics may now be summarised as follows.

Dye-stuffs may be subdivided into seven main groups, namely (1) acid dyes, (2) basic or tannin dyes, (3) direct or substantive dyes, (4) mordant dyes, (5) vat dyes, (6) developed or ingrain dyes, (7) sulphur dyes. In some cases a given dye may fall into two or more of these categories.

Acid Dyes.—These are chiefly the sodium salts of sulphonic acids and of nitrophenolic dyes. They are absorbed directly on wool from a bath which has been acidified with acetic or sulphuric acid. Dyes of this group have very little affinity for cotton even if used with mordants, and they do not yield lakes with tannin. An example of an acid dye is *naphthol yellow S*.



Basic or Tannin Dyes are usually salts of colour bases with hydrochloric acid or zinc chloride, *e.g. magenta, rhodamine B, malachite green*. They are mainly employed for cotton with the aid of tannin mordant, although they can be readily attached directly to wool.

Direct or Substantive Cotton Dyes.—The discovery of direct cotton dyes was made by Böttiger in 1884. The majority of them are salts of azo-compounds derived from benzidine or similar bases. They are soluble in water and dye cotton and cellulose rayon directly from a bath containing sulphuric acid. Direct cotton dyes are in general not as brilliant as the basic dyes, nor as fast as mordant dyes. They are more liable to injury during the finishing processes and are also sensitive to impurities in the material. A typical dye of this group is *Congo Red*.

Mordant Dyes.—In this class are found a large number of dyes of widely differing chemical types; most of them are acidic in nature and all form lakes with mordants. The methods of attaching them to the fibre vary considerably with the nature of the dye and of the material. The most important application of mordant dyes is to wool which has been mordanted with chromium, copper, iron or aluminium. Examples are *alisarin* and many of its derivatives. The chief use with cotton is in the preparation of *Turkey Red*.

Vat Dyes are insoluble in water, hence they cannot be employed directly for dyeing but must first be reduced to a soluble leuco-form. Reduction is commonly effected by means of alkali and sodium hyposulphite, $\text{Na}_2\text{S}_2\text{O}_4$, and owing to the strongly alkaline bath vat dyes are applied to cotton rather than to woollen goods. This disadvantage can be overcome by special methods (see indigosols and solubilised indanthrene). The leuco compounds are soluble in alkali and in this form are readily absorbed by the fibre. The treated material is then allowed to stand in air when the leuco compound is oxidised back to the original dye-stuff, which remains firmly embedded in the cloth. Very fast colours of almost any desired shade can be obtained in this group. Examples of vat dyes are *indigo, indanthrene* and various *anthraquinone derivatives*.

Developed Dyes, Ingrain Dyes. Under this heading are included all those dyes, the last stage in the production of which is carried out on the fibre itself. Mordant dyes are excepted and form a separate group. Three main types of developed dyes are recognised:

(a) *Ice colours*, which are generally used on cotton. They are prepared by impregnating the material with the secondary component of an azo-dye, *e.g. alkaline β -naphthol*; the cloth is then dried and immersed in a cooled bath of a diazonium salt, *e.g. p-nitrobenzene-diazonium chloride*, $\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{N}_2\text{Cl}$. In this example the azo-dye *p-Nitraniline Red* is produced. Various modifications of the process are in use, all of which give very fast ingrained colours.

(b) The material is first dyed with a direct cotton dye containing an amino group. The dye is then diazotised on the cloth and coupled (developed) with a secondary component to form an azo-dye.

(c) *Aniline black* process. In this method aniline black is produced either by (1) impregnating the cloth with aniline salt, followed by treatment with an oxidising agent, or (2) heating the cloth with a solution of aniline hydrochloride to which has been added either potassium bichromate and hydrochloric acid or potassium chlorate and a vanadium salt as catalyst.

Sulphur Dyes.—These are complex dyes containing sulphur, which are insoluble in water but soluble in aqueous sodium sulphide. They are prepared by heating various amino compounds, *e.g.* *p*-phenylene-diamine, with sodium sulphide and sulphur, thus yielding *sulphur blacks*. The sulphur dyes are applied to cotton by use of aqueous sodium sulphide as solvent, followed by oxidation in air or other suitable treatment.

XVII

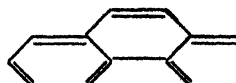
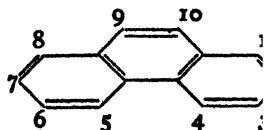
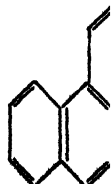
Phenanthrene Group

Phenanthrene, as already stated on p. 591, is found with its structural isomeride anthracene in the anthracene oil of coal tar. After purification of the crude anthracene by means of pyridine bases or solvent naphtha the phenanthrene, owing to its greater solubility, remains in the mother liquors, from which it is isolated. The two hydrocarbons may also be separated by the use of carbon disulphide, or by partial oxidation, which results in anthracene being first attacked.

In the pure state phenanthrene forms white glistening plates, m.p. 101° and b.p. 340° . It dissolves very easily in ether and benzene to give blue fluorescent solutions.

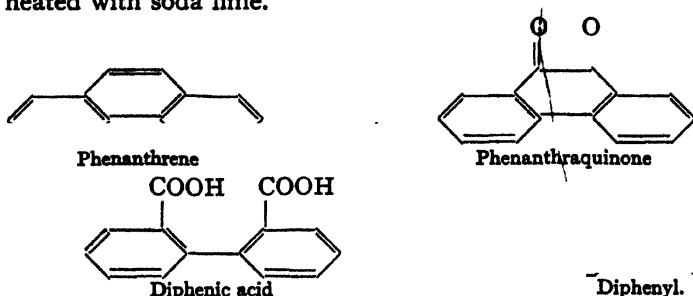
The production of phenanthrene is of small technical importance since all efforts to make use of it in the dye-stuff industry have been fruitless. Interest in phenanthrene chemistry has been quickened in recent years by researches proving the existence of a close relationship between the hydrocarbon and certain important natural products such as plant alkaloids and the steroids (*q.v.*). In the former series it has been established that morphine, codeine, and thebaine contain a phenanthrene nucleus, and further that morphine and codeine are derived from tetrahydro-phenanthrene, and thebaine from a dihydrophenanthrene.

Constitution and Synthesis of Phenanthrene



Like anthracene, phenanthrene is a condensed ring compound, but, whereas in the former the three benzene rings are linear, in phenanthrene the angular arrangement obtains. The formula may conveniently be written in two ways (I and II) and was assigned as the result of oxidative and synthetic methods (Fittig and Ostermayer, Graebe and Glaser).

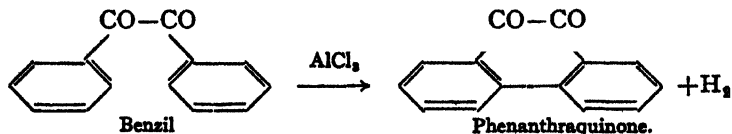
As will be seen from the formula, phenanthrene may be regarded either as a derivative of diphenyl or of naphthalene. Its relationship to naphthalene is shown by syntheses such as No. 3 given below. Oxidation of phenanthrene clearly shows it to be a derivative of diphenyl. When phenanthrene is oxidised with chromic acid it first yields phenanthraquinone and then diphenic acid (p. 548), which is converted into diphenyl when heated with soda lime.



Hence it must be derived from diphenyl in such a way that the group C_6H_5 is attached to each benzene ring in an *o*-position to the bond linking the nuclei. The conversion of phenanthraquinone and its derivatives into derivatives of diphenyl-methane or fluorene, as described on p. 551, also supports this deduction. Further confirmation is obtained from syntheses.

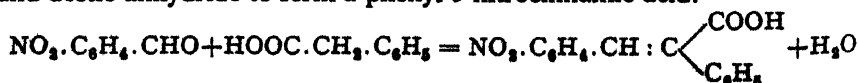
There are many methods available for the synthesis of phenanthrene. A number of these, however, are of historic interest only. The following are of structural or preparative value.

1. Phenanthraquinone is obtained in 25 per cent. yield by dehydrogenation of benzil by the *Scholl process* ("baking" with aluminium chloride at 120°).

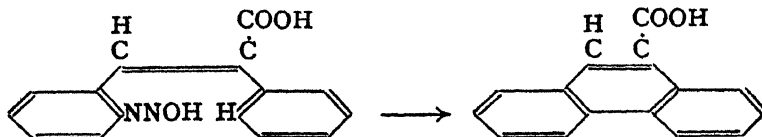


2. A general method, developed by Pschorr for preparing phenanthrene and its derivatives without employing high temperatures, is based on Perkin's reaction (p. 531).

o-Nitrobenzaldehyde is heated with a mixture of sodium phenylacetate and acetic anhydride to form α -phenyl-*o*-nitrocinnamic acid.



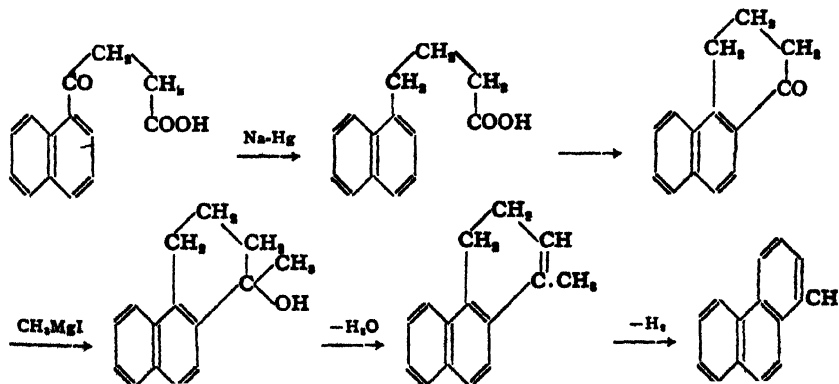
This is reduced to the amino-compound, which when diazotised and shaken in sulphuric acid solution with copper powder, gives nitrogen, water and phenanthrene-9-carboxylic acid. The latter loses carbon dioxide on distillation and is converted into phenanthrene.



This procedure is adapted to the preparation of a large number of phenanthrene derivatives, since in place of nitrobenzaldehyde and phenylacetic acid we may also employ their substitution products. The Pschorr reaction has also been extensively used in the synthesis of other polycyclic aromatic hydrocarbons.

Windaus¹ introduced a modification of Pschorr's synthesis. Whereas Pschorr utilises the condensation product of *o*-nitroaldehydes and phenylacetic derivatives, Windaus employs the products obtained from the unsubstituted aldehydes and oxindole. In the former case the nitrogen required for ring closure is present in the aromatic aldehyde; in the latter it is contained in the phenylacetic acid derivative (oxindole). Windaus was thus enabled to synthesise phenanthrene derivatives (*e.g.* 9-methylphenanthrene, m.p. 91°) which he had isolated as degradation products of the alkaloid colchicine.

3. R. D. Haworth and his co-workers introduced a method which has proved very effective in the synthesis of phenanthrene derivatives.² The method is exemplified by the condensation of naphthalene with succinic anhydride in presence of aluminium chloride to give a mixture of 1- and 2-naphthoylpropionic acids which may be separated. Such acids can then be reduced by the Clemmensen method and the resulting naphthylbutyric acid cyclised (85 per cent. sulphuric acid). Reaction with methyl magnesium iodide gives a carbinol which is then dehydrated



¹ A. Windaus and co-workers, *Ber.*, 1924, 57, 1871, 1875.
workers, *J.*, 1932 and subsequently.

² R. D. Haworth and

and dehydrogenated to a methylphenanthrene. Modifications of the method have led to the synthesis of a large number of substituted phenanthrenes.

Fine Structure of Phenanthrene.—There are several possible bond formulæ for phenanthrene, two of which are given on p. 609 (II and III). These undoubtedly are contributing forms to the resonance hybrid, with form II the more stable and predominating structure. This is in accord with the Fries rule (p. 571) that in polynuclear compounds the bonds are so arranged that each ring tends to possess a benzenoid rather than a quinonoid arrangement of double bonds. In the two examples given it is seen that in II all the rings contain the benzene system of three double bonds, while in III one of the rings has a quinonoid structure. The chemical properties of phenanthrene are therefore best given by formula II.¹

Chemical Behaviour of Phenanthrene and its Derivatives.—The most reactive positions in phenanthrene are 9 and 10. In other words the 9:10-“bridge” is attacked by reagents much more easily than the rest of the molecule and, as we have seen, is also easily ruptured with the formation of diphenyl derivatives (see p. 610). 9:10-Phenanthraquinone is obtained from the hydrocarbon by oxidation, 9:10-dihydrophenanthrene (m.p. 94° to 95°) by reduction with hydrogen in the presence of platinum black, and the 9:10-dibromide by reaction with bromine in presence of peroxides.² The bromination of phenanthrene has already been discussed owing to its bearing on the mechanism of aromatic substitution (p. 438).

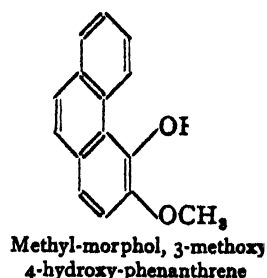
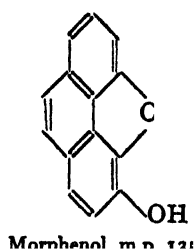
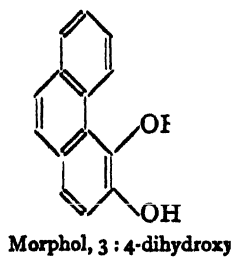
From the established formula of phenanthrene may be derived five different monosubstitution products, corresponding to the positions 1, 2, 3, 4 and 10. It will readily be seen that the hydrogen atoms in the “bridge” are similarly situated; hence the 9- and 10-substitution products are the same.

A comparatively large number of disubstitution derivatives is theoretically possible, and with still further substitution the number of isomerides increases in a manner alarming to the experimenter. The preparation of phenanthrene derivatives by direct substitution is accordingly a matter of difficulty; the products so obtained generally contain several monosubstitution products in addition to unchanged hydrocarbon and disubstitution products. The one exception is the preparation of 9-bromophenanthrene, which is readily formed by the bromination of the hydrocarbon in the presence of a catalyst such as ferric bromide. On the other hand sulphonation at 60° yields a mixture of 1-, 2-, 3- and 9-monosulphonic acids.

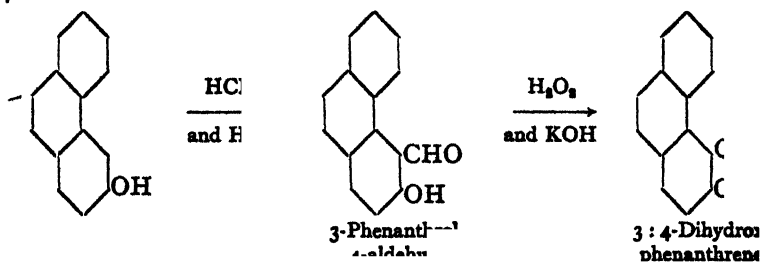
Hydroxyphenanthrenes.—Certain hydroxy-derivatives of phenanthrene such as *morphol* and *morphenol* are important degradation products of morphine and its methyl ether codeine.

¹ For further support of this formula see Fieser and Young, *J.A.C.S.*, 1931, 53, 4120.
² Kharasch, White and Mayo, *J. Org. Chem.*, 1937, 2, 574.

Morphol is a disruption product of morphine in which no nitrogen is present. It was prepared from morphine methiodide by heating with acetic anhydride, and for long could only be identified generally as a dihydroxy-phenanthrene. Subsequently, some information as to the position of the hydroxyl groups was obtained from the observation that



the dihydroxy-phenanthraquinone prepared from morphol possessed dyeing properties similar to those of alizarin, and hence should contain the hydroxyl groups in the ortho-position (see p. 598). After the relationship between morphol and morphenol had been made clear by reducing the latter to the former, the structure of 3:4-dihydroxy-phenanthrene was proposed for morphol. Confirmation of this formula was supplied by the synthesis of dimethyl-morphol described below, and later by Barger's synthesis of morphol itself. Dimethylmorphol (3:4-dimethoxyphenanthrene) was synthesised by applying the Pschorr method to 2-nitro-3:4-dimethoxybenzaldehyde. This synthesis establishes the 3:4-positions of the two methoxy groups, as it is improbable that any intramolecular rearrangement could take place under the experimental conditions used. The synthesis of morphol was effected from 3-phenanthrol-4-aldehyde (obtained by the interaction of 3-phenanthrol, hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride) by treating it with hydrogen peroxide and potassium hydroxide in aqueous pyridine solution.¹ The morphol or 3:4-dihydroxy-phenanthrene obtained melted at 44°.



Dimethyl-morphol crystallises from alcohol in colourless leaflets, m.p. 44°.

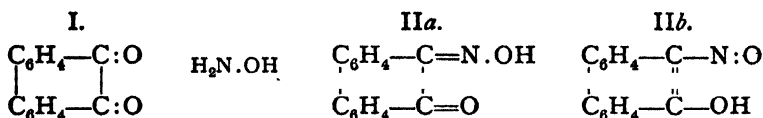
¹ This reaction has been shown by H. D. Dakin to be a general method of converting hydroxy derivatives of benzaldehyde and acetophenone into polyhydric phenols.

The synthetic 3:4-dimethoxy-phenanthrene is identical with the dimethyl-morphol prepared from methyl-morphol, a degradation product of codeine.

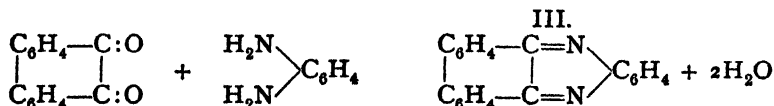
Morphenol (p. 613), which represents the molecular skeleton of morphine and thebaine, yields on fusion with alkali 3 : 4 : 5-trihydroxy-phenanthrene, m.p. 148°.

Phenanthraquinone and its Derivatives

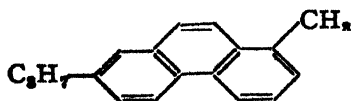
Phenanthraquinone, $C_{14}H_8O_2$ (formula I below), is generally prepared by oxidising phenanthrene with chromic acid in glacial acetic acid solution. It crystallises in orange-coloured needles, m.p. 208°. When a solution of phenanthraquinone in glacial acetic acid is treated with sulphuric acid and toluene containing thiotolene (see index), a blue-green coloration is developed; after dilution with water and extraction with ether the colour changes to violet (*Laubenheimer's reaction*). As already indicated under β -naphthaquinone, it is closely related to the α -diketones in its properties. With hydroxylamine it forms, according to conditions, a monoxime (m.p. 160°) or a dioxime. The former exhibits tautomerism, reacting according to either of the formulæ IIa, or IIb.



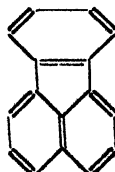
Phenanthraquinone, like other α -diketones, reacts with o -diamines to give phenazine derivatives. Thus with o -phenylene diamine it condenses to form *phenanthraphenasine* (III) :



Retene is present in certain fossil coniferous resins found in deposits of peat and brown coal. It is formed by the dry distillation of the wood of conifers, and can therefore be obtained from pine tar. Part of the retene in these sources probably originates from the diterpene derivative **abietic acid** (m.p. 153°), which has been isolated from resin or colophonium (p. 405) and yields retene on being heated with sulphur.



Retene, methyl-isopropyl-phenanthrene, m.p. 98°



Fluoranthene, 1:2-benzacenaphthene, m.p. 110°.

A hydrocarbon isolated along with phenanthrene from "Stupp" fat is fluoranthene¹ (see annexed formula). It is generally obtained from coal tar.

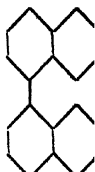
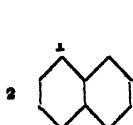
Phenanthrene like the other polynuclear aromatic hydrocarbons has a planar molecule. R. D. Haworth and G. Sheldrick pointed out, however, that in 4:5-dimethylphenanthrene there will be interference between the methyl groups, and this can be clearly seen by inspection of a scale drawing or model of the molecule. This interference must lead to distortion of the molecule either by the methyl groups no longer being in the plane of the aromatic rings or by the aromatic rings ceasing to be planar. In either case molecular dissymmetry will result and this has been demonstrated by the resolution of 4:5:8-trimethylphenanthrene-1-acetic acid into an optically active form.² "Molecular overcrowding" can be caused by the overlapping of hydrogen atoms since a 3:4-5:6-dibenzphenanthrene-9:10-dicarboxylic acid derivative has been resolved.³

XVIII

Other Hydrocarbons containing Condensed Nuclei

In addition to naphthalene, anthracene and phenanthrene, a number of hydrocarbons of still higher molecular weight are known containing condensed benzene rings, many of which occur in the fraction of coal tar boiling above 360°. These may be described very briefly.⁴

In recent years a number of hydrocarbons of this type have been prepared synthetically. Scholl has shown that the condensation of aromatic nuclei with loss of hydrogen—a process long known in the form of pyrogenic reactions—is greatly accelerated in the presence of aluminium chloride. In this way condensation can be satisfactorily effected at as low a temperature as 100°, and the method can therefore be applied to substances which could not survive the drastic conditions of a pyrogenic reaction. The practical details have been worked out particularly for the union of aromatic nuclei in cases where elimination of hydrogen leads



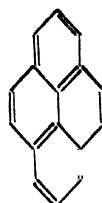
Perylene.

¹ See *The Chemistry of Fluoranthene* by S. H. Tucker and M. Whalley, *Chem. Reviews*, 1952, 50, 483. ² M. S. Newman and L. Hussey, *J.A.C.S.*, 1947, 69, 3023. ³ F. Bell and D. H. Waring, *Chem. and Ind.*, 1949, 321. ⁴ See also *Aromatische Kohlenwasserstoffe*, E. Clar. *Natural Products related to Phenanthrene*, L. F. and M. Fieser (New York, 1949). J. W. Cook, *Ann. Reports*, 1942, 39, 155.

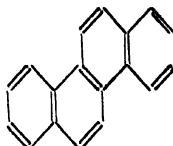
to the formation of new rings. Thus α -iodonaphthalene has been converted into 1:1'-dinaphthyl, and the latter by heating with aluminium chloride (*dry bake*) gave perylene, $C_{20}H_{12}$, which was obtained in the form of yellow or bronze leaflets of m.p. 264° to 265° .

The formulæ for some of the better-known compounds of this type are given below.

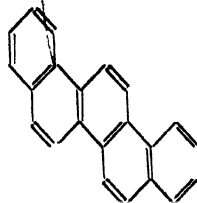
According to the manner in which the benzene nuclei are fused together there may be formed molecules of a linear type such as pentacene or angular ones such as chrysene or picene. Isomeric compounds of these two types differ markedly in their properties. Thus 1:2:5:6-dibenzanthracene (see p. 617) is colourless, whereas pentacene is dark blue. The reactivity of the meso positions in anthracene towards oxidising and reducing agents is diminished by the fusion of other benzene nuclei at the angular positions, but is increased when these are attached so as to form linear compounds.



Pyrene, $C_{16}H_{10}$
m.p. 148°



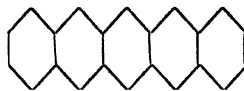
Chrysene, $C_{18}H_{12}$
m.p. 250°



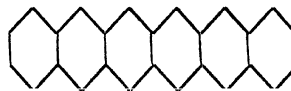
Picene, $C_{22}H_{14}$
m.p. 364°



Naphthalene
 $C_{10}H_8$ (Red)

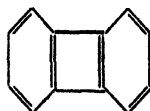


Pentacene
 $C_{22}H_{14}$ (Dark blue)



Hexacene.
 $C_{26}H_{16}$ (Green)

The cyclic compounds which we have already encountered are composed of five-membered or six-membered rings. Biphenylene, prepared by Lothrop,¹ is the first known example of an aromatic compound containing a four-membered ring. Its *cyclobutadiene* structure has been confirmed by electron diffraction and X-ray investigations.²



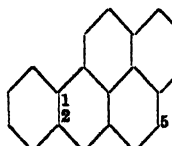
Biphenylene

Carcinogenic Compounds³

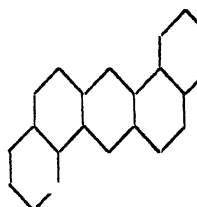
It is well known that continued contact with certain tars may lead to the development of cancer, but only within the last few years has information become available regarding the nature of the compounds

¹ W. C. Lothrop, *J.A.C.S.*, 1941, 63, 1187. ² J. Waser and V. Schomaker, *ibid.*, 1943, 65, 1451. J. Waser and Chia-Si Lu, *ibid.*, 1944, 66, 2035. ³ See J. W. Cook, *Chemistry and Cancer* (Institute of Chemistry), 1943.

which may give rise to the disease. Progress in this field is largely due to the work of Cook, who showed that 1:2-benzpyrene,¹ a complex aromatic hydrocarbon present in tar, possesses very strong carcinogenic properties. Another hydrocarbon of similar nature which has been synthesised by Cook is 1:2:5:6-dibenzanthracene. Various other compounds of this kind have been prepared, the molecules of which all contain the condensed ring system of phenanthrene. The physiological effect is, however, strongly dependent upon the molecular structure. Thus 4:5-benzpyrene and 1:2-benzanthracene are almost entirely

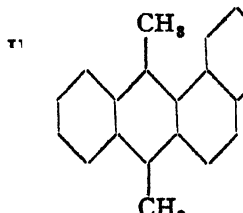
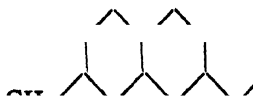


1:2-Benzpyrene



1:2:5:6-Dibenzanthracene.

The most potent carcinogenic compounds so far discovered are 20 methyl cholanthrene, I, which is a simple transformation product of the deoxycholic acid of bile (see p. 628), and 9:10-dimethyl-1:2-benz



XIX

Non-benzenoid Aromatic Hydrocarbons²

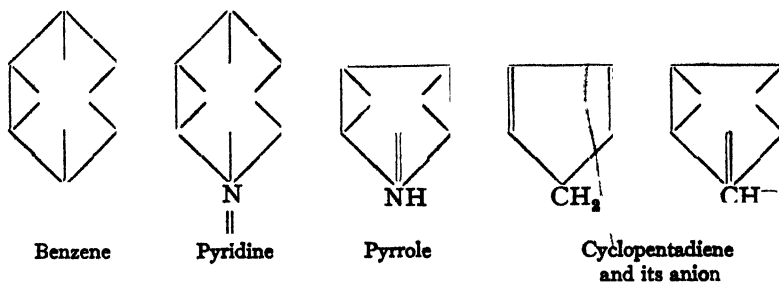
The main features of benzene are that it possesses a planar hexagonal molecule and a stability quite at variance with its valence-bond formula of alternating single and double bonds and totally distinct from the reactivity of the corresponding open-chain triene. This stability is attributed to the non-localisation of the six π -electrons and the attendant decrease in their energy (or increase in the resonance energy of the molecule). It is therefore natural to enquire if there are other planar cyclic compounds, whose valency-bond formulæ contain conjugated double bond systems, but which possess a stability quite different from

¹ J. W. Cook, C. L. Hewett and I. Hieger, *Nature*, 1932, 130, 926; *J.*, 1933, 395.

² W. Baker, *Non-benzenoid Aromatic Hydrocarbons*, *J.*, 1945, 258.

that of the open-chain analogues: in short, which show a considerable degree of resonance and exhibit the so-called "aromatic properties" of benzene. Such an enquiry is pertinent since the problem, which had for many years been studied in a rather desultory manner, has recently been intensively investigated and has yielded significant and interesting results.

Bamberger pointed out in 1893 that if the centric formula for benzene be adopted similar formulæ can be ascribed to other substances such as pyridine and pyrrole provided the nitrogen atom is regarded as pentavalent.



Pyridine and pyrrole are thus heterocyclic analogues of benzene and their stability in consequence is not surprising. Indeed these formulæ correspond to modern ideas provided each line is regarded as a π -electron.¹ Structurally related to pyrrole is the five-membered ring compound cyclopentadiene which is a typical diene, whose lack of aromaticity is shown by its small resonance energy (*ca.* 3 kcal./mole), very similar to that of the open-chain analogue. Cyclopentadiene, however, forms very stable metallic salts and this stability is again traceable to a resonating electron sextet in the anion. The stability of the cyclopentadienyl anion is even more convincingly shown by iron dicyclopentadienyl which is so stable that it remains unchanged even when heated to 470°.²

The cyclopentadienyl anion thus provides us with a non-benzenoid aromatic hydrocarbon, *i.e.* a cyclic unsaturated hydrocarbon stabilised by resonance. Other analogous mono- and di-cyclic hydrocarbons suggest themselves as possibly possessing aromatic stability. The simplest system is that of cyclobutadiene, which has not yet been prepared, but which in all probability is highly unstable. Cycloheptatriene (tropilidene)



¹ J. W. Armit and R. Robinson, *J.*, 1925, 1604. F. R. Goss and C. K. Ingold, *J.*, 1928, 1268. ² G. Wilkinson, M. Rosenblum, M. C. Whiting and R. B. Woodward, *J.A.C.S.*, 1952, 74, 2125.

is highly unsaturated and has only a small resonance energy. Cyclo-octatetraene (p. 391) has been prepared and in spite of its cyclic system of conjugated double bonds is very unsaturated. Its lack of aromaticity is attributed at least in part to the non-planarity of the molecule.

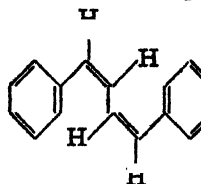
Of the dicyclic hydrocarbons the simplest is *pentalene* (butadiene derivatives being excluded). This hydrocarbon has not yet been prepared, but there is evidence that it is non-aromatic in behaviour. This is confirmed by the properties of a derivative, *dibenzopentalene*, which has recently been prepared.¹ This compound does not form a picrate or a derivative with 2:4:7-trinitrofluorenone. It polymerises easily and behaves like a conjugated diene. Altogether its chemical behaviour is not significantly



Pentalene



Dibenzopentalene

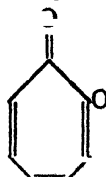


Diphenylbutadiene

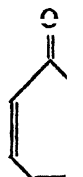
different from that of the corresponding open-chain compound *cis*:*cis* 1:4-diphenylbutadiene. There is thus no evidence to suggest that pentalene is aromatic in character.

Tropone and the Tropolones²

In 1945 M. J. S. Dewar suggested that certain naturally occurring substances, stipitatic acid and colchicine, are derived from the (then unknown compound tropolone. He further suggested that this cycloheptatriene compound should be stable and exhibit many of the characteristics of aromatic compounds. Later work has only served to confirm



Tropolone



Tropone

these conclusions. It should be pointed out that simultaneously and independently Nozoe and his colleagues in Japan were carrying out fundamental work on the tropolones which became generally known only after the War was over.³

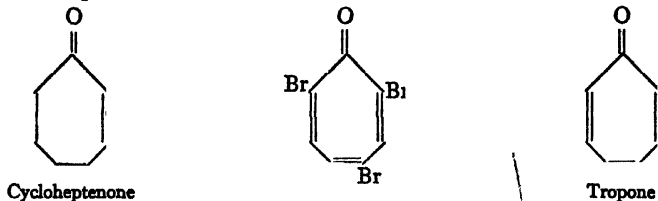
The fundamental aromatic unit of this type of compound, however, is not tropolone but the ketone tropone. Tropolone is therefore a hydroxy-derivative of tropone and the two compounds are related as phenol is to benzene. We shall therefore consider first tropone and then tropolone.

¹ C. T. Blood and R. P. Linstead, *J.*, 1952, 2263. ² J. W. Cook and J. D. Loudon, *Quart. Rev.*, 1951, 5, 99. A. W. Johnson, *Science Progress*, 1951, 39, 495. ³ T. Nozoe, *Nature*, 1951, 167, 1055. A. J. Birch, *Ann. Reports*, 1951, 48, 185.

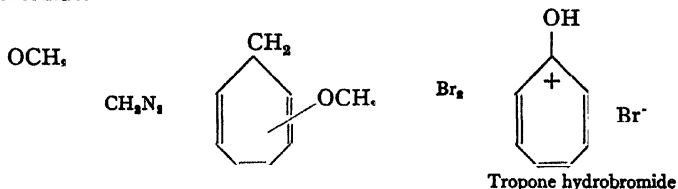
Tropone

Tropone, *cyclohepta-2:4:6-trien-1-one* (formula given above), has been prepared by two methods which are typical of those used to prepare cycloheptatriene compounds of this type.

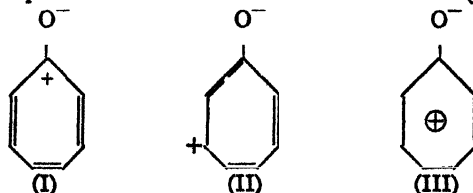
(1) Cycloheptanone with bromine yields 2:4:7-tribromotropone, which on treatment with hydrogen and a palladium-barium sulphate catalyst in the presence of potassium acetate undergoes hydrogenolysis to yield tropone.¹



(2) In the second method anisole and diazomethane are irradiated by ultra-violet light.² The process may be pictured as the addition of a methylene radical to the anisole, followed by rearrangement to a cycloheptatriene derivative. This on oxidation with bromine yields tropone hydrobromide.



The assigned structure of tropone has been confirmed by reduction of tropone to cycloheptanone. There is good evidence to show that this formula must be modified to contain a polar carbonyl group and that it is a resonating compound with contributing structures such as (I) and (II). It is best represented by formula III which indicates that the tropone ring contains 6 π -electrons in a cyclic resonating system and should therefore possess considerable aromatic character (see below).



This picture of the tropone molecule is in harmony with its chemical and physical properties. Tropone has a dipole moment and its boiling-point

¹ H. J. Dauben, Jr., and H. J. Ringold, *J.A.C.S.*, 1951, 73, 876.

² W. von E. Doering

and F. L. Detert, *ibid.*, 1951, 73, 876.

is much higher than that of the isomeric benzaldehyde. These facts as well as infra-red data provide evidence for the highly polar carbonyl group, whose presence accounts for the formation of salts such as the hydrobromide already discussed.

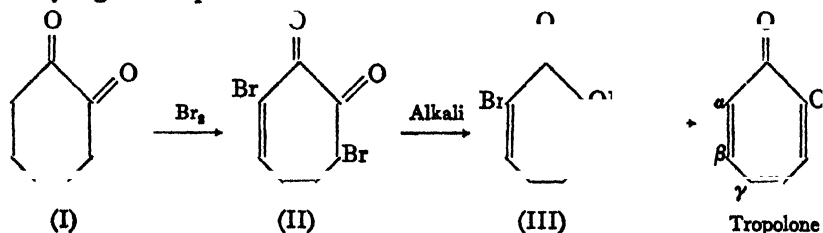
Tropone behaves partly as an unsaturated compound. It decolorises aqueous permanganate and forms a Diels-Alder adduct with maleic anhydride. On the other hand it exhibits benzenoid characteristics in forming 2:4:7-tribromotropone on bromination and 2-aminotropone on amination. These properties and the fact that tropone in contrast to cyclopentadienone has been isolated show the stabilising effect of the π -electron sextet.

Tropolones

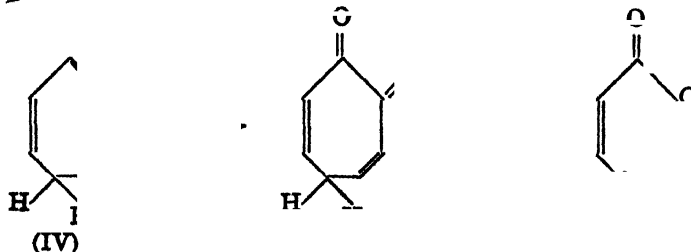
Tropolone derivatives occur in nature and include stipitatic acid, colchicine, purpurogallin, and α -, β -, and γ -thujaplicins. Many others have been synthesised.

Like tropone the tropolones may be synthesised either from cycloheptane derivatives or by the ring-expansion of aromatic compounds. The use of both methods may be illustrated by considering the synthesis of the parent compound tropolone.

Cycloheptanone is oxidised by selenium dioxide to cycloheptanedione (I), bromination of which under suitable conditions yields the dibromo-product (II). The bromo-compound is converted by alkali into a bromo-tropolone (III), hydrogenolysis of which with a palladium-charcoal catalyst gives tropolone.¹



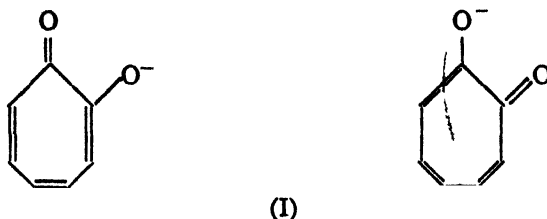
In the second method benzene and diazomethane are exposed to ultra-violet light to give a product, probably cycloheptatriene (IV). Oxidation of this compound with potassium permanganate yields tropolone which is purified through its copper complex.²



¹ J. W. Cook, A. R. Gibb, R. A. Raphael, and A. R. Somerville, *J.*, 1951, 1, 3. ² W. von E. Doering and L. H. Knox, *J.A.C.S.*, 1950, 72, 2305.

Tropolone may be prepared by the oxidative degradation of purpurogallin and as this provides a reasonably cheap and plentiful starting material the method is of practical value in spite of the several stages involved.¹

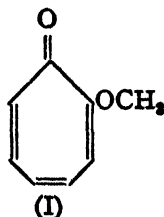
The tropolones are crystalline solids, which may be purified by sublimation. The monocyclic compounds are colourless, but the unsubstituted benzotropolones are yellow and purpurogallin is red. As enols they form crystalline acetates and benzoates and form salts with alkali. These salts are more deeply coloured than the parent compounds and this is due to the increased resonance of the anion (I). The enolic



character is also shown by the green colour which tropolone gives with ferric chloride. It forms chelate compounds with copper and ferric ions.

Tropolone is amphoteric. It is an acid, pK_a 6.7, intermediate in strength between phenol and acetic acid. Its basic properties are shown by the formation of a crystalline hydrochloride.

Methylation of tropolone is effected by diazomethane, dimethyl sulphate, or methanol and hydrogen chloride. The resulting ether is readily hydrolysed. Both the formation of the ether by the action of methanol and hydrogen chloride and its ready hydrolysis suggest that the methyl compound behaves to some extent as an ester. This might be expected from the theory of vinylogy (p. 572) since the carbonyl and methoxy groups are separated by three conjugated double bonds (I).

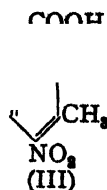
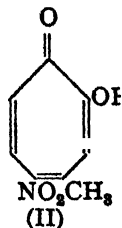


The carbonyl group is inert and does not react with hydroxylamine, etc.

The tropolones undergo a type of benzilic acid rearrangement in which the tropolone is changed to a benzenoid derivative. This is

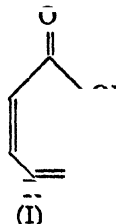
¹ R. D. Haworth and J. D. Hobson, *J.*, 1951, 561.

exemplified by the conversion of the methylnitrotropolone (II) to 3-methyl-4-nitrobenzoic acid (III).



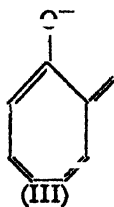
The method is obviously of value in determining the structures of substituted tropolones.

Dewar forecast that the tropolones would show many of the characteristics of aromatic compounds and this has been borne out by experience. The ring is resistant to oxidation as shown by the oxidative method of preparation (p. 621). Tropolone undergoes substitution when attacked by electrophilic agents. Bromination gives tribromotropolone, while nitrous acid and nitric acid give γ -nitroso (I, R = NO) and γ -nitro tropolone (I, R = NO₂) respectively. Benzenediazonium chloride also



couples in the γ -position and on reduction gives γ -aminotropolone which behaves like a primary aromatic amine, undergoing diazotisation, etc.

In agreement with these aromatic properties are the findings of Robertson¹ that tropolone has a planar regular heptagonal structure with C—C bond lengths of 1.4 Å. Tropolone has also a resonance energy of about 29 kcal. per mole. The resonance energy and the consequent stability of tropolone result partly from interaction of the carbonyl and the hydroxyl groups so that important structures in addition to that represented on p. 621 are II, III, etc. It would appear that tropolone



can adequately be represented by formula IV in which seven p -orbitals are occupied by six electrons.²

¹ J. M. Robertson, *J.*, 1951, 1222. ² W. von E. Doering and L. H. Knox, *J.A.C.S.*, 1951, 73, 828; 1952, 74, 5683.

Azulenes¹

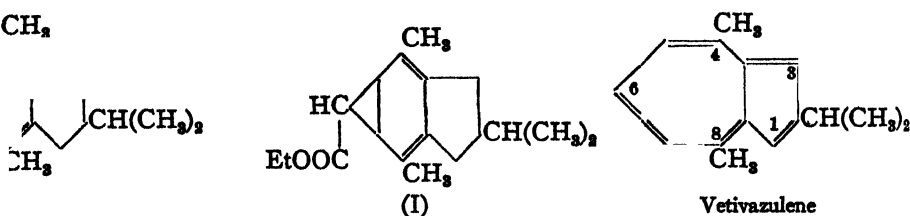
Another bicyclic system which, like pentalene, contains a fully conjugated double bond system is azulene, which contains a five-membered ring fused to a seven-membered ring and is isomeric with naphthalene. Unlike pentalene, azulene and many substituted azulenes have been prepared and investigated largely as a result of the pioneer work of Ruzicka and of St Pfau and Plattner, who were the first to formulate the azulenes correctly.²

The azulenes are of great interest from the theoretical stand-point and differ from other dicyclic aromatic hydrocarbons by their intense blue, violet, or green colours. Their stability and chemical properties show that they are distinctly aromatic in type and this is confirmed by azulene possessing a resonance energy of about 45 kcal./mole.

The azulenes occur in or are obtained from constituents of certain essential oils. Azulene is also obtained as a by-product in the preparation of cyclooctatetraene and decalin. They are isolated by making use of their basic properties and extracting them with phosphoric acid. Subsequent dilution with water suffices to generate the azulenes, often in the pure state. They may be characterised and purified by converting them into their picrates or trinitrobenzene derivatives and breaking these down into their components by passing their solutions down a column of alumina (see p 90).

Of the methods used to synthesise the azulenes two call for mention here.

(1) *Ring-enlargement of Indan Derivatives*.—This approach is exemplified by the interaction of 2-isopropyl-4:7-dimethyl-indan (isopropylidimethyl-hydrindene) and diazoacetic ester. Addition occurs at CH_2

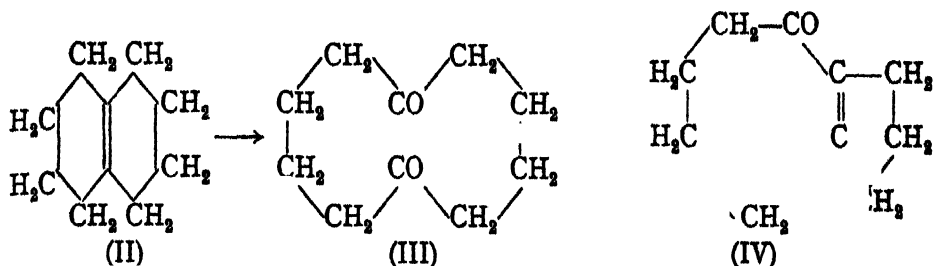


a double bond and a pseudoacetic ester (I) is formed. Successive hydrolysis, decarboxylation, and dehydrogenation is accompanied by ring-enlargement to yield vetivazulene, identical with the natural product from vetiver oil. It should be mentioned that a good method for the dehydrogenation of hydrogenated azulenes to the azulenes is still lacking.

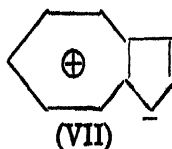
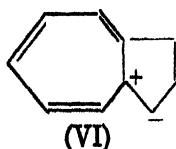
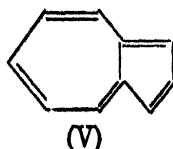
(2) *From Dicyclic Hydrocarbons containing Ten Ring-carbon Atoms*.—The dehydration of β -decalol is accompanied by isomerisation and the unsaturated hydrocarbon (II) is obtained. This hydrocarbon is ozonised

¹ Reviews: H. Pommer, *Zeit. angew. Chem.*, 1950, 6a, 281. R. D. Haworth, *Ann. Reports*, 1937, 34, 393. M. Gordon, *Chem. Rev.*, 1952, 50, 127. ² A. St Pfau and Pl. Plattner, *Helv. Chim. Acta*, 1936, 19, 858.

to the diketone (III), which in the presence of a catalyst such as sodium carbonate undergoes an internal condensation to give the azulene derivative (IV). Reduction followed by dehydrogenation affords azulene. This method is used to synthesise 4-substituted azulenes since the keto group can react with Grignard reagents, and alkyl or aryl groups can thus be introduced into the molecule.



The azulenes, containing as they do planar bicyclic systems of fully conjugated double bonds are, as has already been stated, aromatic in character. Their stability is shown by the fact that they can be isolated from naturally occurring sources or obtained as dehydrogenation products. They do not undergo autoxidation and they do not polymerise. Like naphthalene they form molecular compounds with picric acid, etc. and recently it has been shown that azulene undergoes electrophilic substitution under mild conditions in the 1-position, and 1-acetyl-, 1-chloro-, 1-bromo-, and 1-nitro-azulene have been obtained.¹ The stability of azulene (resonance energy 46 kcal./mole) arises from its resonance in forms such as V and betaine structures such as VI,² giving a resultant resonating molecule which may be formulated as VII.¹ Structure VII accounts



not only for the stability of the azulene molecule but also for its colour, basicity, etc.

Azulene undergoes isomerisation to naphthalene as might be anticipated, since naphthalene has a considerably higher resonance energy.

¹ A. G. Anderson, Jun., J. A. Nelson, and J. J. Tazuma, *J.A.C.S.*, 1953, 75, 4980. ² W. H. Stafford and D. H. Reid, *Chem. and Ind.*, 1954, 277.

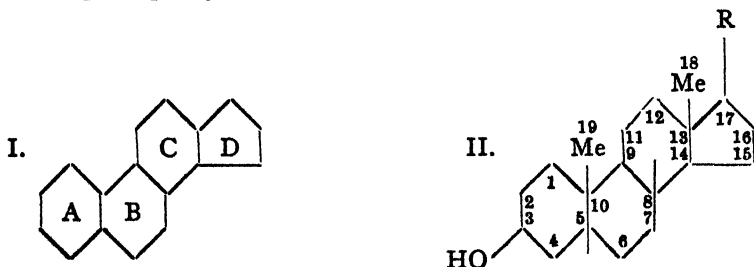
XX

Steroids¹

Under the heading of steroids are included several important groups of natural products such as the sterols, bile acids, sex hormones, cardiac poisons and saponins. These compounds, believed to be related to the polyterpenes, are derived from a *cyclopentanoperhydrophenanthrene* (I)—*per* meaning completely saturated—containing a fused structure of one 5-membered and three 6-membered rings. The majority of the steroids conform to the generalised formula II² and have a hydroxyl group in position 3, although in some this group is missing and others are ketonic or polyhydroxy in type. They vary considerably in the degree of hydrogenation of the rings and in the nature of the residue R attached to position 17 as shown in the following table.

Steroid		Variations of R
Sterols		$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}(\text{CH}_2)_2\text{CHMe}_2 \text{ or similar group} \\ \\ \text{CH}_3 \end{array}$
Bile acids . . .		$-\text{CH}(\text{CH}_2)_2\text{COOH}$ or similar group
Sex hormones :		
Oestrogenic . . .		$-\text{OH}$ or $>\text{CO}$
Corpus luteum . . .		$-\text{COCH}_3$
Androgenic . . .		$-\text{OH}$ or $>\text{CO}$
Cardiac poisons . . .		Lactone ring
Adrenal substances . . .		$-\text{CO}\cdot\text{CH}_2\text{OH}$, etc.

In the cardiac poisons the methyl group (19) may be replaced by the CHO or CH₂OH group.



Elucidation of the constitution of the steroids proved to be a formidable task and many were the problems which confronted Wieland, Windaus, Ruzicka and the other pioneers. The determination of the structure of the nucleus, the size of the component rings, the positions of side-chains, substituents, and double bonds, and the stereochemical complications

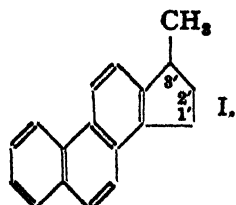
¹ For general references see L. F. Fieser, *Natural Products related to Phenanthrene*, 3rd ed., New York, 1949; W. H. Strain, "The Steroids," in "Organic Chemistry" (ed. H. Gilman), 2nd ed., p. 1340; C. W. Shoppee, *Ann. Reports*, 1946, 43, 200; J. W. Cornforth, *ibid.*, 1953, 50, 216. ² Unless otherwise indicated the rings in these formulae are understood to be saturated. Nuclear hydrogen atoms are omitted for the sake of clearness.

each demanded a vast amount of experiment and great technique. In the following pages only the barest outline can be given to illustrate the physical and chemical methods, often novel and ingenious, used.

Structure of the Nucleus

The structure of the steroid nucleus was derived entirely from the investigations of the sterols and bile acids which Wieland and Windaus showed possessed identical nuclei. This generalisation made possible more rapid progress than might otherwise have been expected. It was clearly an advantage that evidence derived from (say) cholesterol could be applied to the bile acids and *vice versa*. The intimate relationship between the sterols and the bile acids was first definitely established by Windaus who showed that coprostanol, the saturated alcohol derived from cholesterol, could be converted into the hydrocarbon coprostane ($\text{CHOH} \rightarrow \text{CHCl} \rightarrow \text{CH}_2$), which on cautious oxidation broke down into acetone and cholanolic acid from which the bile acids are derived. This discovery first proved the chemical identity of the ring systems in the sterols and bile acids and the nature and point of attachment of the side-chain in the bile acids.

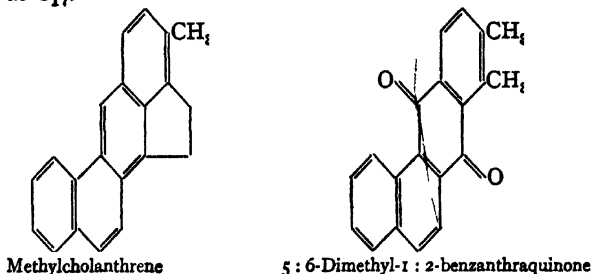
These and other results, especially when the formula of the saturated compound cholestane is taken into account, led to the belief that the nucleus contained a fusion of four rings. In 1927 Diels dehydrogenated cholesterol with palladised charcoal at 500° and obtained chrysene (p. 616), but with selenium under milder conditions he obtained chrysene and a hydrocarbon $\text{C}_{18}\text{H}_{16}$, generally known as the Diels' hydrocarbon. Cholesteryl chloride and cholic acid likewise with selenium at $340\text{--}360^\circ$ yielded the Diels' hydrocarbon, the importance of whose constitution was fully realised and led to intensive investigation by a number of workers. Various formulæ were advanced but proved unsatisfactory until the above-mentioned 1:2-cyclopentano-perhydro-phenanthrene structure was advanced in 1932 by Rosenheim and King and independently about the same time by Wieland. Final confirmation of the Rosenheim-Wieland structure was given by the synthesis by Kon and co-workers¹ of 3'-methyl-1:2-cyclopentenophenanthrene (I), which was proved to be identical with the Diels' hydrocarbon by an examination of derivatives, absorption spectra, and crystal spacings. It is clear that under more vigorous conditions a catalytic enlargement of the five-membered ring also occurs by absorption of the methyl group, which is then followed by dehydrogenation to form chrysene.



Cholic acid, one of the bile acids, likewise on selenium dehydrogenation gives among other products the Diels' hydrocarbon.

¹ G. A. R. Kon, S. H. Harper and F. C. J. Rumicka, *J.*, 1934, 124.

The formation of the Diels' hydrocarbon is suggestive but not conclusive evidence of the presence of a cyclopentanoperhydrophenanthrene nucleus since the yields obtained are very small. Stronger evidence came from the conversion of the two bile acids, cholic acid and deoxycholic acid, to methylcholanthrene whose structure follows from its oxidation to 5:6-dimethyl-1:2-benzanthraquinone, which in turn can be oxidised to 1:2:5:6-anthraquinonetetracarboxylic acid. Not only does the formation of methylcholanthrene provide good evidence regarding the constitution of the nucleus, but it also indicates that the long side-chain is situated at C_{17} .



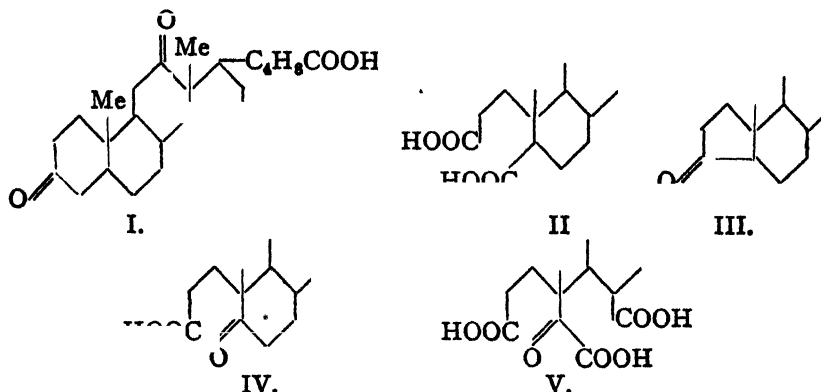
Size of the Rings

This was firmly established as a result of the work on sterols following the formulæ advanced by Rosenheim and Wieland in 1932. But much information bearing on this point had previously been gained, especially by the oxidative degradation of bile acids and their derivatives. Some idea of the mode of attack and of the more important principles involved is given by the following account.

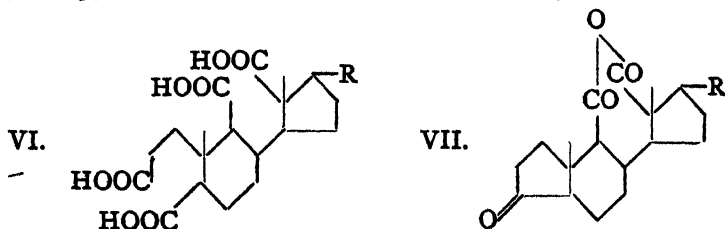
The different hydroxyl and ketonic groups in the bile acids and their derivatives showed graded reactivity (position $3 > 7 > 12$) and use was made of this fact to disrupt one ring without affecting the rest of the molecule. By isolating the resulting tricarboxylic acid or mixture of isomeric acids and studying their behaviour on being heated (see below) it was possible to draw conclusions as to the size of the disrupted ring.

For example, deoxycholic acid (cholic acid, p. 636, with the C_{17} -OH replaced by H) yields **dehydro-deoxycholic acid** (I) on mild oxidation with chromic acid, and under more vigorous treatment the ketonic ring A breaks at the two points indicated to form **deoxybilianic acid** (II) and isodeoxybilianic acid (in II and the following formulæ only that part of the molecule corresponding to rings A and B is shown). The further behaviour of the *bilianic acids*—all bile acid derivatives formed in this manner are termed *bilianic acids*—on pyrolysis (heating in high vacuum or in nitrogen) depends on the relative positions of the carboxyl groups. As has been already mentioned on p. 283 Blanc noted that succinic acid (1:4-positions of carboxyls) and glutaric acid (1:5-) give anhydrides when heated with acetic anhydride, but that adipic acid (1:6-) and pimelic acid (1:7-) lose carbon dioxide and water to form the cyclic

ketones cyclopentanone and cyclohexanone. Windaus and Wieland extended the "Blanc rule" to simple cyclic dicarboxylic acids and then applied it to the bile acid derivatives. Deoxybilanic acid (II), for example, gave rise to a ketonic acid, pyrodeoxybilanic acid (III), with loss of carbon dioxide. The two carboxyls in II are therefore concluded to be in the 1 : 6-positions and to be derived from a six-membered ring in dehydro-deoxycholic acid. On oxidation of acid, III, the ketonic ring is ruptured to form an acid, IV, which on continued oxidation yields a tetracarboxylic acid, norcillanic acid V. The last compound contains only two rings in the molecule.



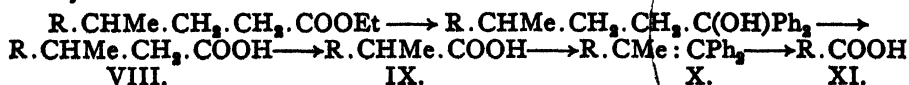
By applying these methods to different types of bile acids it was found possible to open each of the rings A, B and C, although ring D which never contains an attached hydroxyl group, could not be disrupted. Rings B and C, however, gave rise to false deductions on application of Blanc's rule, and it was discovered later that the rule is not reliable in the side chains containing the carboxyl groups are linked to different ring systems. Choloidanic acid, for example (shown in skeleton form in VI), on pyrolysis is converted into VII. Both pairs of carboxyls are



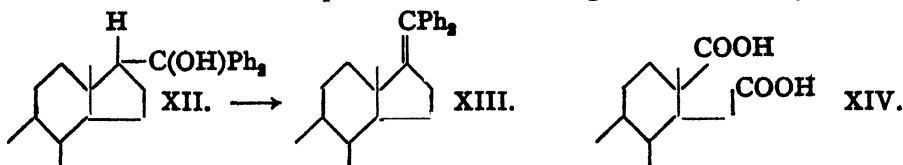
in the 1 : 6 positions, but the pair derived from ring C form an anhydride and it was at one time wrongly concluded that they were therefore of the 1 : 5-type and that ring C was five-membered. It will be seen that these carboxyls are joined to two independent ring systems (B and D), linked only through the single bond between positions 8 and 14.

The most resistant ring, D, was opened by Wieland after cholanic acid (formula, p. 638) had been converted by a step-wise degradation of the side-chain known as the *Barbier-Wieland degradation*, into

ætiocolanic acid. For this purpose cholanic ester was treated with phenylmagnesium bromide (or other Grignard reagent) to form the carbinol, which on oxidation with chromic oxide broke down to benzophenone and *norcholanic acid*, VIII. The term *nor* means lower homologue and the Barbier-Wieland degradation is a means of effecting the change $R.CH_2.CO_2H \rightarrow R.CO_2H$. Repetition of the process yielded *bisnorcholanic acid*, IX, and this by a third application of the Grignard reagent followed by dehydration of the carbinol gave an unsaturated hydrocarbon, X, which on oxidation yielded **ætiocolanic acid**, XI. These reactions are represented by the following equations in which R = the cholane residue $C_{19}H_{31}$; Ph = phenyl; and Me = methyl.



The opening of ring D was then effected in the following steps. Aetiocolanic ester, when treated with phenylmagnesium bromide, formed a carbinol (XII), which was dehydrated to *diphenyl-aetiocolene*, XIII. This olefinic compound on oxidation gave a dicarboxylic acid,



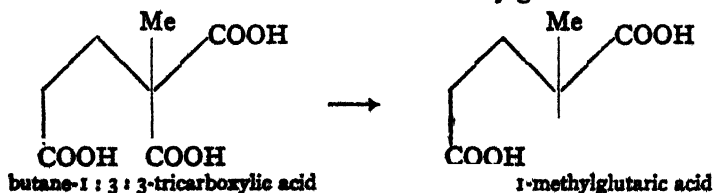
ætiobillanic acid XIV, indicating that ring D had opened. The conversion of ætiobillanic acid into an anhydride on pyrolysis led by application of Blanc's rule to the conclusion that this ring is five-membered.

Further evidence for this comes from the conversion of cholic and deoxycholic acids into methylcholanthrene (p. 628).

Position of the Side-chain

The above Barbier-Wieland degradations of cholanic acid show conclusively that the bile acids contain a $-CHMe.CH_2.CH_2.CO_2H$ chain attached to the nucleus, and the formation of the Diels' hydrocarbon and methylcholanthrene is good evidence that this side-chain is situated at C_{17} . This is in agreement with X-ray and surface tension measurements.

Evidence to show that an *angular methyl group* is attached to C_{10} was provided by oxidation experiments. A side-product of the nitric acid oxidation of desoxycholic acid is butane-1:3:3-tricarboxylic acid which lost carbon dioxide and formed 1-methylglutaric acid.



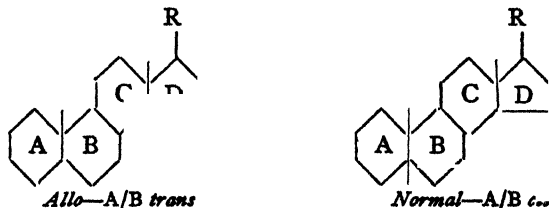
The methyl group is therefore attached to a quaternary carbon atom and since C_{10} is known to be quaternary (see p. 632) we have strong support that the C_{10} atom carries an angular methyl group.

The presence of a second angular group at C_{13} was shown by degradation experiments on desoxycholic acid.

Stereochemistry of the Steroids

Theoretically, the cyclic nucleus of four rings present in the steroids may exist in a number of isomeric forms, since the component rings (if hydrogenated) may be joined together by either *cis* or *trans* linkages as in the *cis* and *trans* decalins (p. 587).

The problem of the configuration of the steroid nucleus is somewhat simplified by the fact that rings B and C, and rings C and D appear in nearly all cases to be fused together by *trans* linkages in the natural steroids. There are therefore two fundamental steroid nuclei: (a) nuclei with *trans* A/B rings and described as *allo* structures, and (b) nuclei with *cis* A/B rings known as *normal* structures. Included in the *allo* series are cholestane, androstane, 5-*allopregnane*, and 5-*allocholane*, while in the other series are coprostanane, testane, pregnane, and cholane.



The convention generally adopted for representing the different configuration of the substituted steroids is that proposed by Fieser and extended by Reichstein and Shoppee. *Position* is specified by the number of the nuclear carbon atom bearing the substituent and *configuration* by the suffixes α and β . These suffixes denote a definite stereochemical orientation: α denotes that the group lies behind the plane of the paper and is shown in formulæ by a broken line, while β denotes a group lying above the plane of the ring and is shown in formulæ by an unbroken line.

Models show that the angular groups attached to C_{10} and C_{13} in both types of steroid nuclei are similarly orientated and the groups are conventionally assumed to lie above the plane of the ring. Most of the steroids have a hydroxyl group at C_3 and many have others in different parts of the molecule. These hydroxyl groups may be attached either *cis* or *trans* to any given reference point such as the nearest angular group. For example, the hydroxyl group in cholesterol, cholestanol, and coprostanol is denoted by 3 β , signifying that it is situated at C_3 and is *cis* to the C_{10} -methyl group: in *epi*cholesterol, *epi*cholestanol,

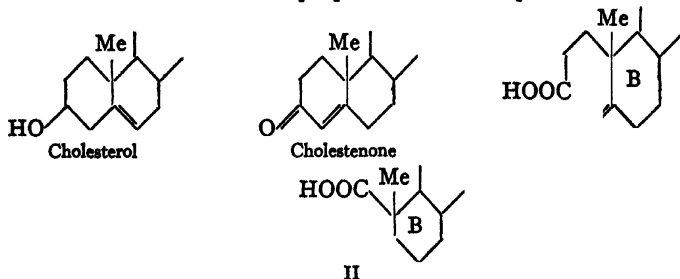
and *epicoprostanol*—*epi* denoting the epimeride of the normal or common form—it has a 3 α configuration showing that it is likewise situated as C $_3$, but is *trans* to the C $_{10}$ -methyl group.

It is impossible to give here the chemical and physical evidence which determined the configuration of the steroid nucleus or of the nuclear substituents. The important conclusion was drawn from X-ray examination of cholesterol and other steroids by Bernal that the steroid molecule has a flat structure. Ruzicka pointed out that this can only occur if rings B and C are joined by *trans* linkages. From degradation experiments it is also concluded that C and D are fused together in the same manner.

Position and Configuration of the Hydroxyl Group in Cholesterol, etc.

The position of the hydroxyl group in cholesterol was shown by several degradations of which the following is representative.

Oxidation of cholesterol with aluminium *tert.*-alkoxides and a large excess of acetone (*Oppenauer* oxidation) gives the ketone cholestenone, oxidation of the secondary alcoholic group to the corresponding ketone being accompanied by a change in position of the double bond (see formula). Since cholestenone shows an absorption band with a maximum of 240 $m\mu$ the carbonyl group and the double bond are in all probability conjugated, the double bond occurring in the 4:5-position. This formula for cholestenone satisfactorily accounts for its oxidation products including the keto-acid I. In this acid the carboxyl group is shown to be separated by two methylene groups from the ring B by Clemmensen reduction, followed by *two* applications of the Barbier-Wieland degradation to give the acid II. This has all the properties of a compound containing a

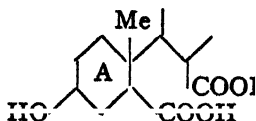


carboxyl group attached to a quaternary carbon atom, *i.e.* it loses carbon monoxide readily when heated with sulphuric acid and is not easily esterified. The structure of acid I therefore seems to be established, and, since the carboxyl group is at the site of the carbonyl group in cholestenone, the hydroxyl group in cholesterol must be situated at C $_3$.

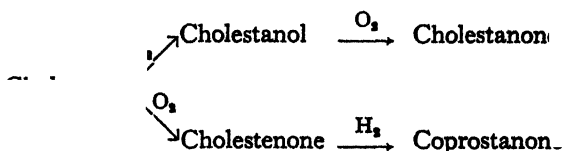
A correlation of the hydroxyl compounds of the cholesterol and bile acid groups was effected through investigations on *hyodeoxycholic acid* which Windaus proved to be 3:6-dihydroxycholanolic acid. By partial oxidation of the acid Wieland and Dane converted it into 3-hydroxy-6-ketocholanolic acid, which on reduction gave 3-hydroxy-*allocholanolic*

acid owing to allomerisation having taken place at C_5 through the influence of the adjacent keto group. This acid is isomeric with lithocholic acid and proved to be identical with the hydroxy*allo*cholic acid previously obtained by Windaus from cholesterol. This incidentally provides additional evidence that the hydroxyl group in cholesterol occupies position 3.

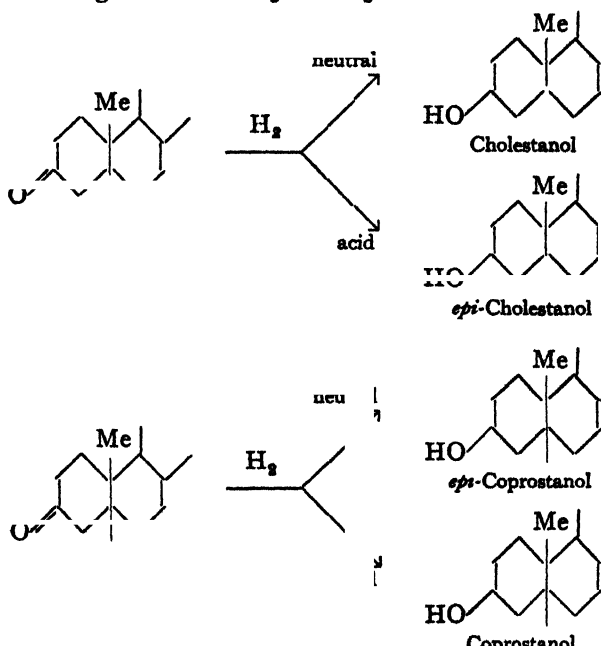
Shoppee showed the hydroxyl group in cholesterol to be β -orientated by converting cholesteryl acetate into the acid shown in the annexed formula. Support is obtained in this way for the conclusions reached by other though less decisive experiments, among which may be outlined Ruzicka's work on the catalytic reduction of the saturated ketones



cholestanone and coprostanone. These ketones are both obtained from



Reduction by catalytic hydrogen gives the four possible saturated sterol with different configurations at C_3 and C_5 .



The configurations assigned are based on the *Auwers-Skita rule* according to which neutral media favour reduction to *trans* forms and acid media to *cis* forms. Neutral reduction gives cholestanol in which the C₃-hydroxyl group is *trans* to the C₆-hydrogen atom and acid reduction gives *epi*-cholestanol in which the relationship is *cis*. Similarly in coprostanol and *epi*coprostanol the relationships are *cis* and *trans* respectively. Confirmation of the configurations thus assigned comes from epimerisation experiments of the above four sterols with sodium ethoxide. The resulting mixtures contain predominately the *trans*-sterols in conformity to the generalisation that *trans* compounds are more stable than *cis*.

It will be noted that the β -configuration of the C₃-hydroxyl group in cholestanol (dihydrocholesterol) is in agreement with that assigned by Shoppee to the same group in cholesterol.

A characteristic property of the 3 β -hydroxy steroids is their precipitation with digitonin, a glycoside of the saponin group. The α - or *epi*-compounds do not form such complexes and this specific reaction, discovered by Windaus, has proved very useful in steroid chemistry for determining the configuration of the hydroxyl group in position-3. Cholesterol, cholestanol, coprostanol, and ergosterol are among the steroids precipitated by digitonin, while the α -compounds not precipitated include the *epi*-derivatives, the bile acids, and androsterone.

Sterols

Sterols are complex alcohols found in many animal and vegetable oils and fats, partly in the free state and partly in the form of esters. From these sources they are isolated by hydrolysis with alcoholic potassium hydroxide, followed by extraction with ether or light petroleum. Sterols are extensively distributed in nature and may be regarded as fundamental constituents of all living cells except those of bacteria. They may be classified into three types.

Zoosterols of animal origin, *e.g.* cholesterol and coprostanol.

Phytosterols of plant origin, *e.g.* stigmasterol.

Mycosterols of fungal origin, *e.g.* ergosterol.

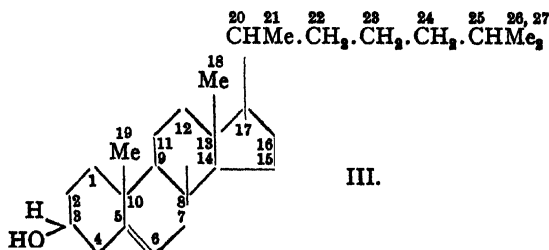
Some of the best known sterols are listed in the following table.

Sterols

		Double Bonds.	m.p.	[α] _D	Occurrence.
Cholesterol . . .	C ₂₇ H ₄₈ OH	1	149°	-39.5	All animal cells, gall-stones, whale oil, etc.
Cholestanol . . .	C ₂₇ H ₄₇ OH	0	140°	+28.7	Found with cholesterol.
Coprostanol . . .	C ₂₇ H ₄₇ OH	0	101°	+28	In faeces.
Zymosterol . . .	C ₂₇ H ₄₈ OH	2	109°	+47.3	Yeast.
Ergosterol . . .	C ₂₈ H ₄₈ OH	3	165°	-132	Ergot, yeast.
Ostreosterol . . .	C ₂₈ H ₄₇ OH	2	143°	-44	Oysters.
Fucosterol . . .	C ₂₉ H ₄₇ OH	2	124°	-38	Algae.
Stigmasterol . . .	C ₂₉ H ₄₇ OH	2	170°	-51	Calabar and soya beans.

Cholesterol, $C_{27}H_{46}OH$, is an unsaturated secondary alcohol which is widely distributed in the human organism, especially in the brain and nerves. It was first discovered in gallstones, from which it may be prepared. In these sources it is accompanied by the saturated compound, dihydrocholesterol or cholestanol, $C_{27}H_{48}OH$, m.p. 140° . Cholesterol is apparently synthesised in the animal organism, as sterols introduced in the form of food are largely eliminated unchanged. When a solution of the compound in chloroform is treated with sulphuric acid and acetic anhydride a blue coloration results (*Liebermann-Burchard*).

The structure of cholesterol has been established with that of the closely related bile acids, and is represented by formula III ($Me = CH_3$), the rings being fully saturated except for a double bond at 5:6. The presence of a secondary alcoholic grouping was early established by the formation of a mono-acetate and by the production of a ketone, cholestenone (fig. III with CO in place of CHOH and the double bond displaced to 4:5) when cholesterol is oxidised (p. 632). The double bond is proved by the addition of two atoms of bromine and also by hydrogenation in the presence of platinum black to form the saturated

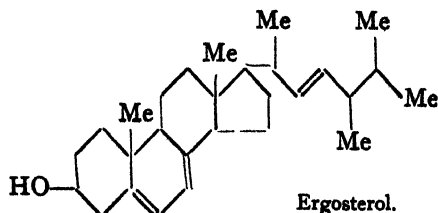


alcohol cholestanol (*dihydrocholesterol*). Further reduction of cholestenone or of cholesterol results in the loss of oxygen and addition of hydrogen to the double bond to give the saturated hydrocarbon cholestane, $C_{27}H_{48}$. The nature of the side chain at position 17 was demonstrated by Windaus's oxidation of cholesteryl acetate with chromic oxide, when disruption occurred with the formation of a volatile ketone, 2-methylheptanone-6, $CH_3.CO.CH_2.CH_2.CH_2.CH(CH_3)_2$, which was isolated by steam distillation. This leads to the structure of the side chain as given in III.

Coprostanol, $C_{27}H_{48}OH$, a saturated dextrorotatory stereoisomeride of cholestanol, is formed in the intestines by bacterial hydrogenation of cholesterol and is therefore present in faeces. On vigorous reduction the hydroxyl group is replaced by hydrogen to give the saturated hydrocarbon coprostanane, $C_{27}H_{48}$.

Ergosterol, $C_{28}H_{48}OH$, m.p. 165° , is an unsaturated alcohol containing the same carbon skeleton as cholesterol, but with an additional methyl group attached to the side chain at position 24, and with

three double bonds at 5:6, 7:8, and 22:23. It was discovered by Tanret in ergot, occurs in various fungi, including yeast, and is present in small amounts in most living tissues. On irradiation with ultraviolet light or sunlight ergosterol is converted into a number of isomerides, accompanied by considerable decomposition. One of these has powerful anti-rachitic properties and is closely related to the vitamin D group (see under vitamins).



The presence of a conjugated system of double bonds in the molecule is shown by the characteristic ultra-violet spectrum of ergosterol. The constitution of the side-chain is established by oxidation. Ergosterol on ozonisation yields the aldehyde, $\text{CHO} \cdot \text{CH}(\text{CH}_3) \cdot \text{CH}(\text{CH}_3)_2$, and partially reduced ergosterol with chromic anhydride gives the ketone $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{C} \cdot \text{CH}(\text{CH}_3)_2$.

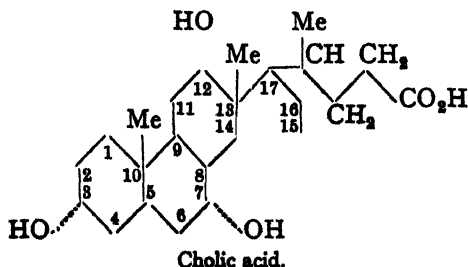
In **Stigmasterol**, $\text{C}_{29}\text{H}_{47}\text{OH}$, the side chain at position 17 is —CHMe .
 $\text{CH} : \text{CH} \cdot \text{CH} \begin{cases} \text{CH}_3 \\ \text{CHMe}_2 \\ \text{C}_5\text{H}_9 \end{cases}$ and the molecule contains a double bond at 5:6.

Both ergosterol and stigmasterol have the same steric arrangement of hydroxyl, methyl groups and long side chain as is present in cholesterol.

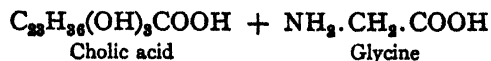
Zymosterol is a cholestadienol containing double bonds at 8:9 and 24:25 and with the side chain $\text{—CHMe} \cdot (\text{CH}_2)_2 \cdot \text{CH} : \text{CMe}_2$ attached to position 17. It is thus the first example of an unsaturated natural sterol devoid of a double bond at the 5:6-position. The terminal isopropylidene group is also unusual, but its presence is shown by the formation of acetone when zymosterol is ozonised. When fully saturated, zymosterol is converted into cholestanol.

The Bile Acids

Bile acids form the main constituents of the bile or secretion of the liver in vertebrate animals, the function of which is to promote the enzymic disruption of fats in the intestine. In this source they exist to



a large extent in peptide union with the amino-acids glycine and taurine, and the resulting glyco- and taurocholic acids possess the physiological advantage of being more soluble in water than the unpaired acids



When the peptide bond is ruptured by enzymic or alkaline hydrolysis the bile acids are liberated as a mixture of acids which varies in composition with the animal species and with seasonal and other factors. All the compounds, however, are saturated hydroxy derivatives of the monocarboxylic acid, *cholanolic acid*, those of most frequent occurrence being **cholic acid** and **deoxycholic acid**. From 100 litres of ox bile Wieland succeeded in isolating 5-6 kg. of cholic acid, 600-800 gm. of deoxycholic acid and only 1 gm. of lithocholic acid.

Cholic acid, $3\alpha:7\alpha:12\alpha$ -trihydroxy-cholanolic acid, $\text{C}_{23}\text{H}_{36}(\text{OH})_3 \cdot \text{COOH}$, is present in the bile of all animals. Deoxycholic acid, $3\alpha:12\alpha$ -dihydroxy-cholanolic acid, accompanies cholic acid in bile and has the property of forming stable co-ordination complexes with varying molecular proportions of other compounds such as palmitic, stearic and oleic acids, and also with hydrocarbons, esters, alcohols, ethers, etc. These addition complexes, which yield colloidal solutions in water, are classed together under the heading of **choleic acids**. The complex with acetic acid (alcohol or ether) contains equimolecular proportions of the two components, but as the molecular weight of the fatty acid rises its proportion in the choleic acid falls. Thus 1 molar proportion of palmitic acid combines with

Bile Acids

Name.	Position of OH groups.	m.p.	$[\alpha]_D$.	Occurrence.
Cholic acid	3 : 7 : 12	196-8°	+35	All animals.
Bufodeoxycholic acid . .	3 : 7 : 12	197°	+37	Toad.
β -Phocaicholic acid . .	3 : 7 : 23	222°	+27	Seal, walrus.
Deoxycholic acid . . .	3 : 12	176°	+55	All animals.
Chenodeoxycholic acid . .	3 : 7	140°	+11	Man, ox, goose, hen.
Ursodeoxycholic acid . .	3 : 7	203°	+57	Bear.
α -Hyodeoxycholic acid . .	3 : 6	197°	+8.4	Hog, hippopotamus.
Lithocholic acid	3	186°	+32	Man, ox.

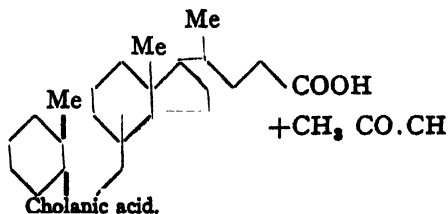
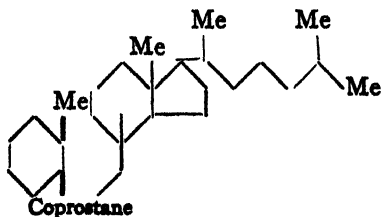
8 molar proportions of deoxycholic acid. The complexes are crystalline and have definite melting points; they are remarkably stable and are not separated into their individual components by solution in water or alkali. Choleic acids containing higher fatty acids can be converted into deoxycholic acid by displacing the fatty acid with acetone, alcohol or ether, using the latter in excess, followed by vaporisation of the combined solvent from the product so obtained.

Lithocholic acid, 3 α -hydroxy-cholanic acid, is found in the bile of man and of cattle and was first isolated by H. Fischer from the gall stones of oxen.

Structure of the Bile Acids

Some of the methods by which the structures of the bile acids have been determined have already been outlined. One of the most useful reactions has proved to be the oxidation of the hydroxy acids to ketonic acids ($\text{CHOH} \rightarrow \text{CO}$) with a cold solution of chromic oxide in sulphuric or acetic acid as reagent. In this manner cholic acid was dehydrogenated by Hammarsten to **dehydrocholic acid**, a triketo-compound. The keto acids are not only readily identifiable by conversion into their oximes, semicarbazones, etc., but may be made to undergo further transformation into the deoxygenated acids such as cholanic acid ($\text{CO} \rightarrow \text{CH}_2$), the formula of which is given below. Another valuable reaction has been the distillation of the hydroxy acids in a high vacuum, when water is eliminated with the production of unsaturated acids ($\text{CH}_2 \cdot \text{CHOH} \rightarrow \text{CH} : \text{CH}$). This change can be carried out in stages according to the number of secondary alcoholic groups in the molecule. The unsaturated acids so obtained may then be hydrogenated catalytically to yield the parent saturated compounds. Thus Wieland succeeded in converting cholic acid into cholanic acid by way of the trebly unsaturated compound cholatrienic acid.

The relationship of the bile acids to the sterols has been demonstrated in several ways. Cholesterol can be converted into coprostanone which on Wolff-Kishner reduction yields coprostanane. This hydrocarbon on cautious oxidation yields cholanic acid, which must therefore contain rings A and B fused together by *cis* linkages. In a similar manner



cholestane is converted into *allocholanic acid*, in which rings A and B must have the *trans* configuration.

Cholic acid, deoxycholic acid, chenodeoxycholic acid, and lithocholic acid are all related to cholanic acid and consequently contain rings A and B in the *cis* position. Hyodeoxycholic acid is 3:6-dihydroxycholanic acid and is obtained in two forms—3 α :6 α and 3 β :6 α . The bile acids contain the 3-hydroxy group in the *trans* position to the hydrogen at C₅ and therefore belong to the α -series. They are regarded as being formed in the organism by oxidative processes from cholesterol, and as the latter compound belongs to the β -series, the mechanism of the biological conversion raises an interesting problem.

Among other reactions, Vesterberg's *dehydrogenation process* has been employed, in which the compounds are heated to a high temperature with sulphur. Generally speaking, this treatment removes hydrogen from hydro-aromatic systems, leading to the formation of well-defined aromatic derivatives (see p. 614 for the conversion of abietic acid into retene). With the sterols and bile acid group, however, it was found preferable to use selenium¹ in place of sulphur, the reaction then proceeding more smoothly and being accompanied by less carbonisation. Angular methyl groups are removed in the process, but nuclear methyl groups remain. The vital significance of the information gained in this way has already been indicated (p. 627).

The Sex Hormones

All the sexual processes of the organism are now known to be initiated and maintained under the stimulus of a number of hormones, each of which can be characterised by definite biological tests. The primary agent appears to be the secretion of the anterior lobe of the pituitary gland, containing the as yet unidentified gonadotropic hormone(s). Under the influence of this secretion other hormones are formed in the ovaries or testes which control the growth and functioning of the reproductive organs. Three main groups of such hormones have been distinguished and the corresponding active principles isolated. In the female these are the **oestrogenic hormones**, which induce the state of oestrus (heat), and the hormones of the corpus luteum (yellow body), which govern the processes of pregnancy. The **male sex hormones** influence the development of the genital tract and accessory male characteristics, such as the comb and wattles of the cock and the horns of the stag. As the result of a brilliant series of researches carried out independently by several groups of workers—mainly in the laboratories of Butenandt, Doisy, Marrian, Ruzicka and their collaborators—it was possible in the brief period of six years to isolate the individual hormones, establish their structures and devise methods of preparing them in sufficient quantities for biological research and use in medicine.

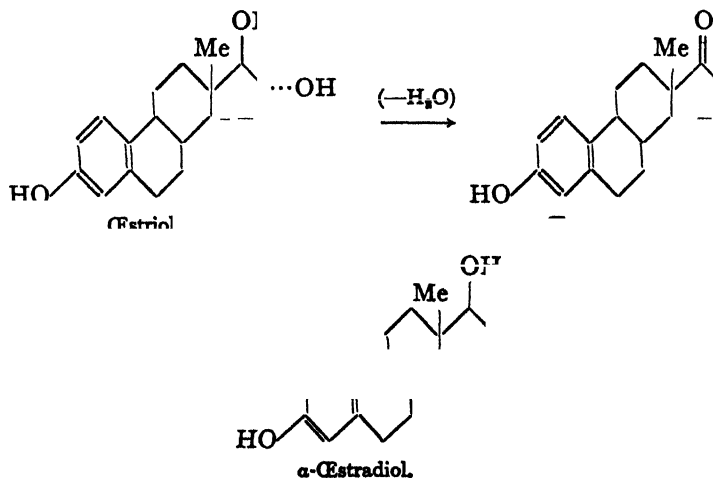
Oestrogenic Hormones.—The first chemical advance was made in this group largely owing to the introduction of the Allen-Doisy test. These workers prepared cell-free extracts of ovaries, which on being injected into castrated mice or rats induced oestrus. The active agent was therefore chemical in nature and with the development of a method of determining the minimum dose necessary for the change a satisfactory quantitative method of estimating the strength of the hormone content (in mouse or rat units) of any given preparation became for the first time possible. The use of this test by Aschheim and Zondek in 1927 led to the important discovery that the hormone, previously obtained in minute quantities and very crude form from the follicular fluid (ovaries), was present in the

¹ O. Diels and A. Karstens, *Ber.*, 1927, 60, 2323.

pregnancy urine of women, from which a much purer active preparation could be obtained by extraction with benzene, preferably after acidic hydrolysis. Shortly afterwards, the isolation of a pure crystalline hormone *œstrone*, was announced independently in 1929 by Doisy in America and Butenandt in Germany.

œstrone, $C_{18}H_{22}O_2$, is a phenolic ketone, m.p. 259° , $[\alpha]_D +170^\circ$. Like so many other members of this group it exists in polymorphic forms. The average content of the urine source is only about 1 mg. per litre (ca. 15,000 m.u. being eliminated per diem) of which only a fraction can be extracted. A better source was discovered in 1930 by Zondek in the urine of pregnant mares (1,000,000 m.u. per diem), and surprisingly enough an even richer one in the urine (1,700,000 m.u. per diem) and testes of stallions. The curious phenomenon of a higher excretion of the female sex hormone by the male is found only among the horse tribe including ass and zebra. Small quantities of the œstrogenic hormones also occur in plants, œstrone having been obtained from palm kernel and the related compound, *œstriol*, from female willow flowers.

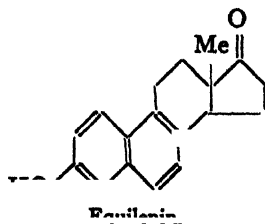
œstriol, $C_{18}H_{24}O_3$, another œstrogenic hormone, was isolated by Marrian in London soon after the discovery of *œstrone*. It melts at 280° , has $[\alpha]_D = +30^\circ$, and shows considerably less œstrogenic activity



than *œstrone* although the effect is more protracted. From the analysis figures Butenandt concluded that *œstriol* was a hydrate of *œstrone* and showed that it could be converted into the latter by heating with potassium hydrogen sulphate followed by distillation in a high vacuum. The relationship was clarified by Marrian and Haslewood, who dehydrated the methyl ether of *œstriol* and obtained the methyl ether of *œstrone*.

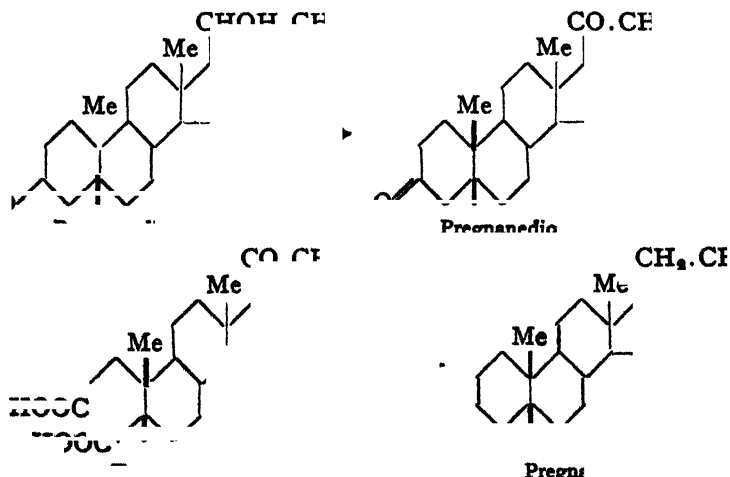
The catalytic reduction of *œstrone* in alkaline medium leads to the formation of *œstradiol-17 β* (α -*œstradiol*) and *œstradiol-17 α* (β -*œstradiol*), m.p. 178° and 223° respectively. The first of these compounds yields an insoluble product with digitonin and is therefore represented as a

β -compound, with OH at C₁₇ in the *cis* position to methyl at C₁₃. α -Œstradiol is an exceedingly potent Œstrogenic compound and is present in the ovaries and in follicular fluid. It is possibly the chief Œstrogenic hormone. β -Œstradiol is comparatively inert.



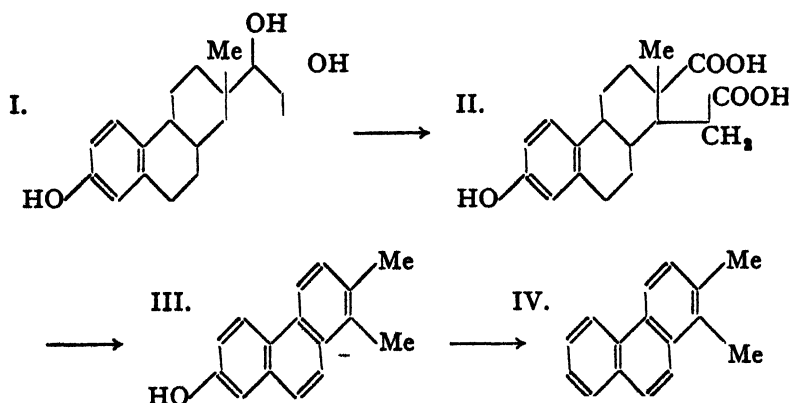
Still other Œstrogenic hormones, equillin, hippulin and equilenin have since been isolated from urine of pregnant mares by Girard in Paris. Equilenin, which is not found in human urine, appears to be formed by the dehydrogenation of Œstrone.

Structures of the Œstrogenic Hormones.—A physiologically inactive companion compound of Œstrone named **pregnanediol** (m.p. 233-235°) was obtained by Marrian in 1929 and was later characterised by Butenandt as a completely saturated substance containing two secondary alcoholic groups, since on oxidation it yielded a diketone *pregnanedione*. Pregnanediol has proved to be a key compound in establishing the chemical structures of this group. Analytical data indicated that the molecule was built up of four fused rings, suggesting a possible relationship to the bile acids. This was borne out by more vigorous oxidation, when the ketone gave rise to a keto-dicarboxylic acid (*cf.* bilianic acids), which on being heated lost carbon dioxide to form a diketone. By Blanc's rule one oxygen was thus deduced to have been attached originally to a 6-membered ring. The other was concluded to be in a side chain, since all three compounds gave the iodoform reaction (*cf.* p. 127).



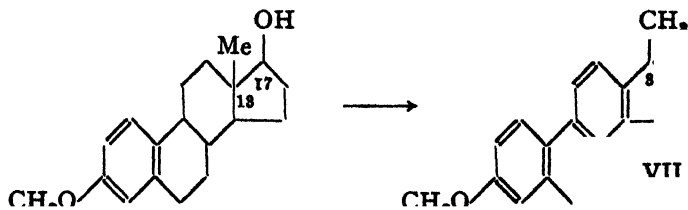
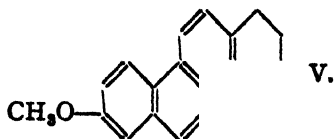
On this basis and by analogy with the sterols and bile acids Butenandt in 1930 expressed the first two of these changes by the above formulæ (here modified according to later views). Subsequently the dione was reduced by the Clemmensen method to a saturated hydrocarbon, pregnane, $C_{31}H_{58}$. The relationship of this compound to the bile acid series was completely established by its synthesis from Wieland's bisnorcholelic ester, by way of the unsaturated hydrocarbon $C_{19}H_{31}.CMe : CPh_2$ (see formula X, p. 630). Butenandt showed that the latter on ozonisation gave the ketone $C_{19}H_{31}.COCH_3$, which on reduction (Clemmensen) was converted into 17-ethyl-*atrcholane*, $C_{19}H_{31}.CH_2.CH_3$, identical in all respects with pregnane. These compounds therefore belong to the coprostane group with rings A and B joined by *cis* linkages. No biological deductions can be drawn from this point, however, because other workers subsequently discovered the stereoisomeric *allopregnanediol* in urine of pregnancy. The position (3) at which the remaining oxygen atom is attached was not determined until later.

In 1932 Butenandt, Marrian and Haslewood advanced a formula for *œstrone* based on the bile acid structures. The last two workers and also Doisy had examined the fusion of *œstriol* (I) with alkali, and shown that a phenolic dicarboxylic acid (II) resulted. Such a change could be explained on the assumption that the two alcoholic hydroxyls in *œstriol* were attached to adjacent carbon atoms, and that a break between these points led to the opening of a ring. The dicarboxylic acid on pyrolysis gave an anhydride and not a ketone, hence the ring is presumably a 5-membered one.



By fusion with selenium Butenandt found that the dicarboxylic acid readily passed into a *dimethyl-phenanthrol* (III), which on distillation with zinc dust yielded 1:2-*dimethyl-phenanthrene* (IV). The same compound has been obtained by selenium dehydrogenation of *œtiobillanic acid*, thus providing a link with the bile acid series. The structure of IV followed from its synthesis by the Haworth method.

More detailed proof, however, was soon supplied by the work of Haworth and of Cook. The former¹ synthesised 1:2-dimethyl-7-methoxy-phenanthrene, which was found to be identical with the methyl ether of Butenandt's compound (III), thus establishing the position of the hydroxyl group. Cook² achieved a remarkable synthesis of 7-methoxy-1:2-cyclopentenophenanthrene (V), containing the fused 5-membered ring; and also isolated this compound from œstrone by methylation, elimination of the ketonic group by reduction, followed by dehydrogenation with selenium. The final points, the positions of the angular methyl group and of ketonic oxygen, were eventually established by Cohen, Cook and Hewett. Methylated œstrone was treated with methyl magnesium iodide, converting the keto group into an alcoholic group; the alcohol VI was then dehydrated (VII) and the resulting unsaturated compound hydrogenated. Final dehydrogenation with selenium gave 7-methoxy-3':3'-dimethyl-1:2-cyclopentenophenanthrene, the structure of which was proved by synthesis. These changes can only be explained by assuming that VI contains a tertiary alcoholic group (at C₁₇) linked to a carbon atom adjacent to a quaternary carbon, when rearrangements such as the wandering of methyl from C₁₃ to C₁₇ are to be expected. This conclusion is confirmed by the fact that a similar migration of a methyl group was observed to occur when œstradiol, which had been methylated in position 3, was dehydrated with zinc chloride and then dehydrogenated, forming 7-methoxy-3'-methyl-1:2-cyclopentenophenanthrene (VIII). In this case the methyl group can only have come from the



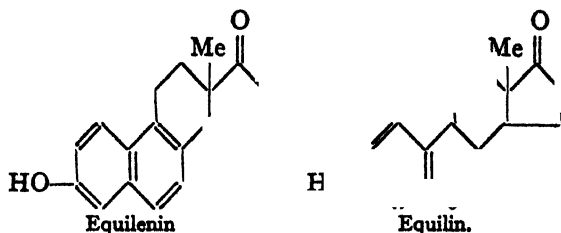
angular position at C₁₃ and must be present as such in œstrone from which the œstradiol was prepared.

The above work of Cohen, Cook and Hewett also threw light on the structures of equilenin and equilin, both of which were converted into 7-methoxy-3':3'-dimethyl-1:2-cyclopentenophenanthrene. Their resemblance to œstrone proves that these hormones have a similar

¹ Haworth and Sheldrick, *J.*, 1934, 864.
J., 1934, 653.

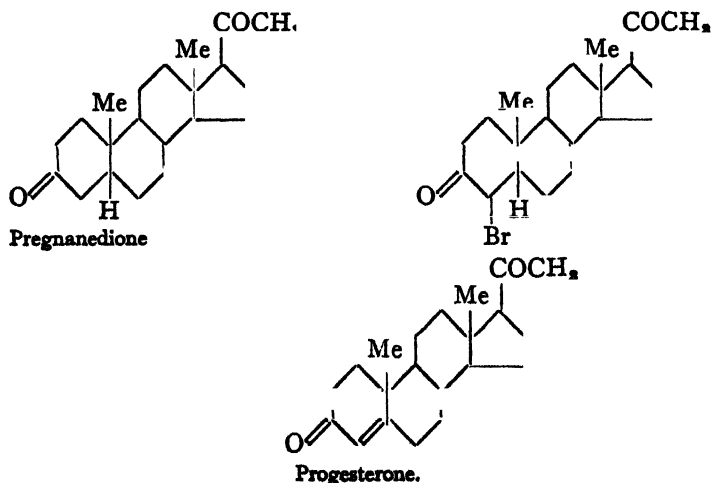
² A. Cohen, J. W. Cook, Hewett and Girard,

arrangement of hydroxyl, methyl and keto groups in a steroid nucleus. Since equilenin forms a picrate it presumably also contains a naphthalene nucleus, leading to the formula given below. This compound was synthesised in its optically active form by Bachmann, Cole and Wilds,



(+)-equilenin proving to be thirteen times as potent as its mirror-image isomeride.¹

Hormone of the Corpus Luteum.—The isolation of the pure crystalline progesterone, $C_{21}H_{30}O_2$, was achieved almost simultaneously in 1934 by Butenandt, Slotta and Allen, using corpus luteum tissue from sow ovaries. Only one hormone appears to exist, but it occurs in two polymorphic forms melting at 128° and 121° . It was found to be an unsaturated diketone and from an investigation of its absorption in



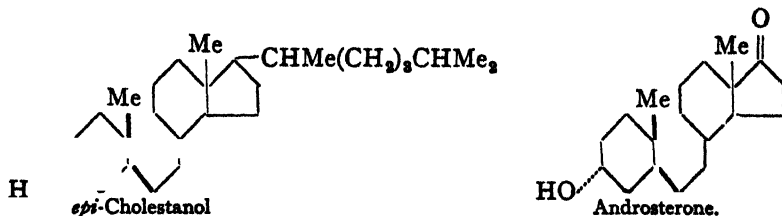
the ultraviolet region it was concluded that it contained a double bond in the $\alpha\beta$ -position to a carbonyl group. An X-ray analysis of the crystalline compound gave results in agreement with a steroid structure, and Slotta formulated the hormone as Δ^4 -pregnene-3:20-dione. This was subsequently confirmed by a synthesis of progesterone from stigmasterol carried out by Butenandt and Fernholz independently. Another and shorter preparation which proves the constitution was made known about the same time by Butenandt. Pregnanediol (see p. 641) was

¹ W. E. Bachmann, W. Cole and A. L. Wilds, *J.A.C.S.*, 1940, 62, 824.

oxidised to the saturated ketone, pregnanedione, which was brominated and hydrogen bromide subsequently removed from the product by heating with pyridine.

The Male Sex Hormones.—The successful isolation of the testicular hormones also rested upon the introduction of quantitative methods of biological assay, by which the activity of a given preparation could be determined. One such method involves injecting the extract into capons, and measurement of the comb growth by use of a shadowgraph (*Gallagher-Koch*); another is based on the effect of injections on the development of the seminal vesicles of castrated immature rats (*Butenandt-Tscherning*).

Androsterone.—Using the above methods of assay, Butenandt and Tscherning in 1931 extracted the first male sex hormone, androsterone, $C_{19}H_{30}O_2$, from male urine which had previously been boiled with hydrochloric acid. The compound, m.p. $182-183^\circ$, proved to be a ketonic alcohol but was only isolated in exceedingly small quantities. On the assumption that it was a steroid, Butenandt suggested a formula which



in 1933 was confirmed and defined in a stereochemical sense by Ruzicka.¹ The latter found that the side chain in cholesteryl acetate could be oxidised away with chromic oxide, and that the acetate of a ketone could be obtained in small yield. On hydrolysis the acetate gave a hydroxy ketone of the structure proposed by Butenandt. The product from cholesterol was not androsterone, but on extending the degradation to the other known stereo-isomers of cholesterol a compound was obtained from *epi*-cholesterol which was identical with the natural hormone. Thus Butenandt's general formula was confirmed and the spatial arrangements of the hydroxyl group and of rings A and B were determined. In this way the relationship between a sex hormone and the sterols was for the first time definitely established.

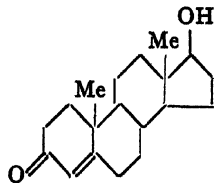
Another preparation of androsterone starting from the more accessible cholesterol was carried out by Marker in the following steps, which must involve at one stage an optical inversion of the group at C3:

Cholesterol \longrightarrow cholesteryl chloride $\xrightarrow{2\text{H}}$ cholestyl chloride (saturated compound) $\xrightarrow{\text{CrO}_3}$ β -chloroandrosterone $\xrightarrow{\text{Potass. acetate}}$ acetyl derivative $\xrightarrow{\text{hydrolysis}}$ androsterone.

Androsterone isolated from urine was found to differ markedly from testicular extract when bio-assays were carried out by the two methods. Equivalent doses of the two extracts as measured by the comb test, did

¹ Ruzicka, *Chem. Rev.*, 1937, 20, 69.

not give equal results with castrated rats, from which the testicular extract appeared to be several times more active. Further investigation led to the isolation from urine of dehydro-androsterone, resembling androsterone in structure but with a double bond in the 5:6-position. This, however, proved even less active as determined by the rat test. Neither of these compounds could therefore be regarded as the chief testicular hormone.



At this stage, in 1935, a crystalline hormone, testosterone, m.p. 154.5° , was isolated from testes by Laqueur and David. It was found to be very potent, but as in the case of the corpus luteum hormone, progesterone, the potency was destroyed by heating the compound with alcoholic alkali. This similarity in chemical properties was traced to a similar (4:5-) position of the double bond, as is seen in the annexed formula due to David.

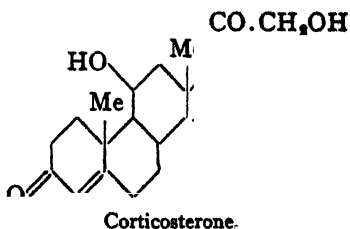
Transmutations of Cholesterol in the Animal Organism

A detailed study of the various steroid derivatives which have been identified in the body or in urine suggests very strongly that they all arise from the biochemical oxidation of cholesterol. Thus the side chain, $-\text{CHMe}^{(a)}\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2^{(b)}\text{CHMe}_2$, may undergo oxidative disruption at point (a), with removal of the isopropylidene group and formation of an acid, $-\text{CHMe}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COOH}$. Subsequent minor alterations in the nucleus can then lead to the production of bile acids. Or the side chain may break at point (b), leaving a group $-\text{CO}\cdot\text{CH}_2$ linked to position 17. The resulting ketone by further metabolic changes may give rise to compounds of the type of progesterone and pregnanediol. As a third possibility, the side chain may be completely oxidised away, leaving a ketonic oxygen atom attached to the nucleus. Such a compound can be readily transformed into testosterone, androsterone and the related œstradiol and equilin groups. There is evidence that such oxidative and reductive reactions actually occur in the body, and schemes representing possible stages by which the hormones and bile acids may be produced from cholesterol have been advanced by Butenandt and by Ruzicka. It is a striking fact that apart from two or three exceptions all the necessary intermediates have already been shown to be present in the organism.

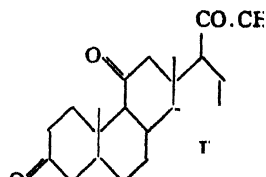
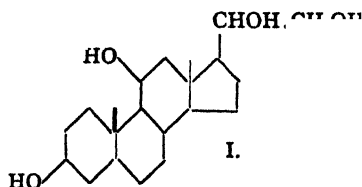
Hormones of the Adrenal Cortex

The secretion from the adrenal cortex, a small gland lying near the kidneys, contains hormones which are essential to life. They play a part in regulating the amount of fluid in the vascular system and appear to be also concerned in sex development. Extracts of the gland are used medicinally in Addison's disease.

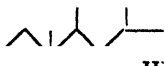
A number of these hormones have been isolated, chiefly by Kendall and Reichstein, the most important one being corticosterone, $C_{21}H_{30}O_4$, a Δ^4 -pregnene-11:21-diol-3:20-dione. The characteristic activity of the compound is largely due to the $CO.CH_2OH$ -group in position 17. Biological activity is found in 21-hydroxy-progesterone, which has been prepared from stigmasterol and differs from corticosterone only in the absence of an 11-hydroxy group.



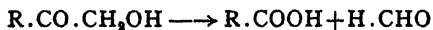
Proof of the steroid structure of corticosterone was provided by its transformation into *allopregnane* in the following steps: The hormone was reduced to the saturated tetrol I (angular methyl groups are omitted): oxidation with periodic acid converted



CH₃.CH



the side chain at 17 into CHO, leaving the rest of the molecule unchanged: treatment with methyl magnesium bromide gave an alcohol ($CHO \rightarrow CHOH.CH_3$), which on oxidation with chromic acid yielded a ketone II: this last when reduced with amalgamated zinc was converted into *allopregnane* III. The formula given above is further supported by the properties of the hormone. Its ultra-violet spectrum shows the presence of an $\alpha:\beta$ -unsaturated ketone fragment. The ketol side-chain was identified by oxidation with periodic acid to one molecule of formaldehyde and one molecule of acetic acid



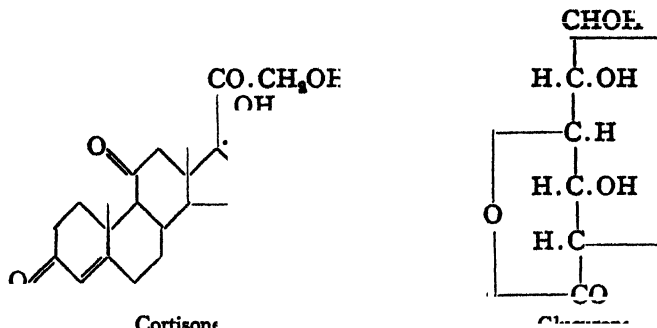
This acid on oxidation yielded a diketone thus showing that in the molecule there must be a secondary alcoholic group in the molecule.

Great interest has been shown in certain substances which have been successfully used in the treatment of arthritis and other rheumatic conditions. Three types of compounds have been claimed to be effective

(1) *Steroids*. The compound of this class which has commanded most attention is **cortisone**, 11-dehydro-17-hydroxy-corticosterone. In the synthesis of this substance difficulty is encountered in introducing an oxygen atom at C_{11} and the ketol side-chain at C_{17} . To be effective substantial doses—about 100 mg. daily—have to be administered to

(2) A substance of quite a different chemical type is the *adreno corticotropic hormone* (ACTH), a protein obtained from pituitary glands

(3) Glucurone, the lactone of glucuronic acid, which probably has the structure shown in the formula.



Cardiac Active Principles

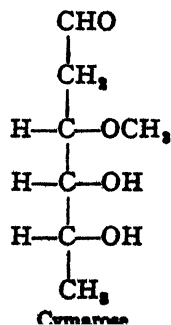
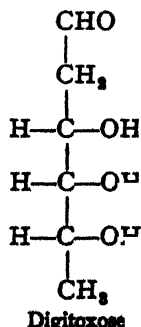
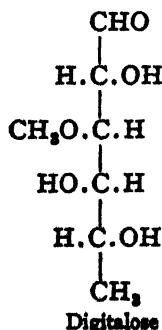
Under this heading are included two groups of compounds :

- (1) Cardiac glycosides of plant origin.
- (2) Toad poisons.

The Cardiac Glycosides

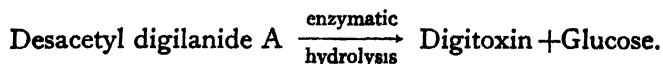
The cardiac glycosides include a number of compounds such as *digitalin* and *strophanthidin*. Some of these are valuable medicinally when employed in small doses by intravenous injection, and lead to a strengthening of the heart action. Larger doses are fatal, causing stoppage of the heart, and certain natural products of this group have been used as arrow poisons by native tribes.

The cardiac poisons occur chiefly in members of the *Apocynaceae* and *Scrophulariaceae*, most of the therapeutically important drugs being prepared from the *Digitalis* (foxglove) group of the latter order. As glycosides, the plant principles are hydrolysed by enzymes or acids to form the corresponding aglycones, known as **genins**, and a mixture of

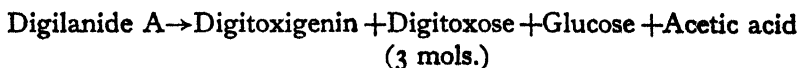


sugars. Amongst the sugars isolated are glucose, rhamnose and a number of others which have not been encountered elsewhere in nature, such as the methylated methylpentose, *digitalose* (3-methyl D-fucose), and various α -deoxysugars, including *digitoxose* and *cymarose*.

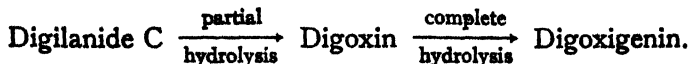
The chemistry of the cardiac glycosides has proved both difficult and arduous. Moreover the separation and isolation of the compounds from the plant has not been easy and the products which were first obtained and thought to be the plant glycosides have been found to be the breakdown products of still more complex glycosides caused by enzymatic hydrolysis. Stoll, however, by taking precautions against enzymatic degradation and using special methods of extraction was able to isolate from *Digitalis lanata* the three natural glycosides **digilanide A**, **B**, and **C**. Each of these can undergo partial or complete hydrolysis as exemplified by the following transformations of **digilanide A**.



Complete hydrolysis may be effected by direct acid hydrolysis as follows



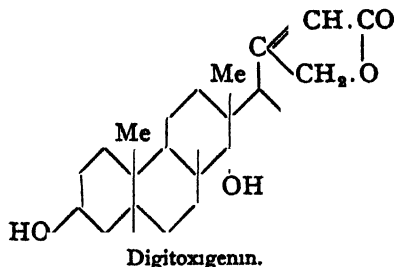
The other digilanides **B** and **C** behave similarly but yield the aglycones *gitoxigenin* and *digoxigenin* respectively.



It may be noted that digitoxin and gitoxin are also obtained from *Digitalis purpurea* (purple fox-glove).

The sugar-free genins were investigated by Windaus and subsequently in greater detail (1922-1934) by W. A. Jacobs. When the structures of the sterols and bile acids were established about 1934, the work of Jacob enabled correct formulæ to be deduced for a number of the more important genins. A typical structure is that shown for **digitoxigenin**, which in addition to hydroxyls at positions 3 and 14, contains at position 1, the lactone ring characteristic of the cardiac poisons. This ring can

be opened by titration with alkali, thus permitting an estimate of the molecular weight of the compound. As can be seen from the formula



digitoxigen contains the steroid nucleus with *cis*-AB and *trans*-BC junctions as in coprostanol. Unlike the sterols, however, the CD junction is *cis*.

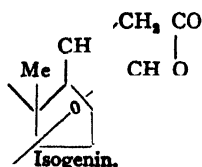
The unsaturated lactonic group is responsible for the deep red coloration given when a genin dissolved in pyridine is treated with an alkaline solution of sodium nitroprusside (*Legal's test*). No such colour is given with the dihydro-genins formed by reduction, in which the lactone ring has been saturated. As a result of the researches of Jacobs it was

thought that the lactone contains the double bond in the $\beta:\gamma$ position with respect to the carbonyl group, but two independent investigations by Elderfield¹ and Ruzicka² indicate that the lactone possesses a $\Delta-\alpha:\beta$ -structure. Since the dihydrogenins prepared from cardiac poison genins retain the ring structure it is concluded that the original genins contain $\alpha\beta$ -unsaturated lactone rings with the β -carbon atoms attached to position 17.

A further peculiarity of the lactone ring is that by the action of alcoholic alkali, it yielded an **isogenin** which no longer gives a coloration with nitroprusside.

In addition to the digitalis compounds there are two other groups of cardiac glycosides: the strophanthus and squill groups.

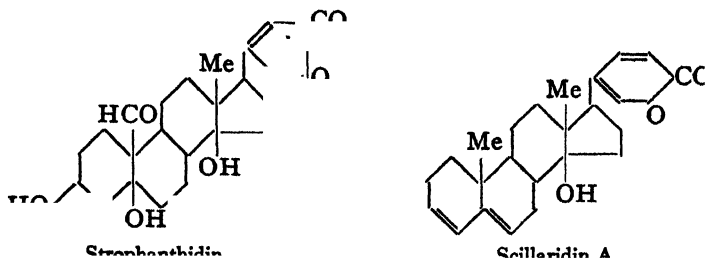
Strophanthidin (from species of *Strophanthus*) contains an aldehyde group in place of the more usual methyl group at position 11, and there is an additional hydroxyl at position 5. The presence of the carbonyl group was shown by the low-intensity absorption at 303 $m\mu$. That this occurs in an aldehydic group was proved by the formation of an oxime; oxidation of strophanthidin to the corresponding acid with neutral permanganate; and the failure of the compound to reduce Fehling's solution. Selenium dehydrogenation of strophanthidin yields the Diels' hydrocarbon (Elderfield and Jacobs, 1934) and this was the first observa-



¹ W. D. Paist, E. R. Blout, F. C. Uhle, and R. C. Elderfield, *J. Org. Chem.*, 1941, 6, 273

² L. Ruzicka, T. Reichstein, and A. Furst, *Helv. Chim. Acta*, 1941, 24, 76. L. Ruzicka, P. A. Plattner, and A. Furst, *ibid.*, 716.

tion to suggest a relationship between the cardiac poisons and the sterols. Conclusive proof of the cyclopentenophenanthrene nucleus in the cardiac poisons was given by Tschesche, who degraded uzarigenin to ætioallocholanic acid. Jacobs and Elderfield similarly degraded digitoxigenin to ætiocholanic acid.



The structures of other closely related compounds are as follows: **gitoxigenin**, 3 : 14 : 16-trihydroxy-10 : 13-dimethyl-; **digoxigenin**, 3 : 12 : 14-trihydroxy-10 : 13-dimethyl-; **uzarigenin**, 3 : 14-dihydroxy-10 : 13-dimethyl- and **periplogenin**, 3 : 5 : 14-trihydroxy-10 : 13-dimethyl-.

Scillaren A is obtained from the white squill or sea onion, *Scilla maritima*, and yields on acid hydrolysis the aglycone **Scillaridin A**, whose formula is given above. Here also is an α : β -unsaturated lactone, which, however, contains a second double bond and a six-membered ring. This lactone is distinguished from the five-membered rings encountered above both by its absorption spectrum and its failure to give the Legal test.

Toad Poisons

Active principles with an action on the heart resembling that of digitalis, although less persistent, have long been known to be present in the parotid glands and skin of the toad (Latin, *bufo*). The secretions of the glands, which are situated behind the eyes, were investigated chiefly by Wieland and found to contain a mixture of **bufotoxins** (conjugated genins), **bufagins** (genins), together with sterols, adrenaline and other alkaloid bases. The cardiac activity arises from the bufotoxins and bufagins.

These compounds are related chemically to the cardiac poison group, being derived from a steroid nucleus having at position 17 a six-membered and generally an unsaturated lactone ring such as is found in Scillaridin A. They are not present in the secretion as glycosides but as suberylarginine esters of the genins. The best characterised compound is **bufotoxin** (from *Bufo vulgaris*), $C_{40}H_{62}O_{11}N_4$, which can apparently lose suberylarginine in the organism to yield **bufotalin**, $C_{26}H_{38}O_6$. With normal hydrolysis, e.g. hydrochloric acid, bufotalin breaks down into **bufotalien**, $C_{24}H_{36}O_5$ (an anhydro-compound), acetic acid and water.

Saponins

Saponins are plant glycosides having the property of forming colloidal solutions with water which foam on being shaken. This definition also includes the cardiac poisons, but owing to their characteristic physiological effects these compounds are grouped separately. Saponins may be recognised by their strong hæmolytic action, even in high dilution, which results in the liberation of hæmoglobin from the red corpuscles of the blood. When taken in small quantities by the mouth they are not poisonous, but they are relatively more harmful to lower organisms and are employed by primitive tribes for poisoning fish without rendering them inedible. Their property of forming insoluble complexes with equimolecular proportions of certain other steroids (as well as various higher alcohols, phenols and thiophenols) has already been mentioned on p. 634. Digitonin has thus proved a valuable if expensive reagent for determining the configuration of hydroxyl attached to the steroid nucleus, especially in position 3.

Saponins are found as mixtures in soapwort (*Saponaria officinalis*), smilax and plants of the gourd family, and in smaller quantities in digitalis plants, where they accompany the cardiac poison glycosides.

From the chemical standpoint the saponins fall into two groups :

(1) Steroid saponins from digitalis plants, which yield Diels' hydrocarbon on dehydrogenation with selenium.

(2) Triterpenoid saponins which on dehydrogenation give 1 : 2 : 7-trimethylnaphthalene (*sapotalene*).

The saponins are glycosides which on acid hydrolysis give *sapogenins* and several molecular proportions of sugars. Some of the best known saponins and sapogenins are given in the following list.

Digitonin, from *Digitalis purpurea*, breaks down to digitogenin, galactose (2 mols.), glucose (2 mols.) and xylose.

Gitonin, from *D. purpurea*, forms gitogenin, galactose (3 mols.) and a pentose.

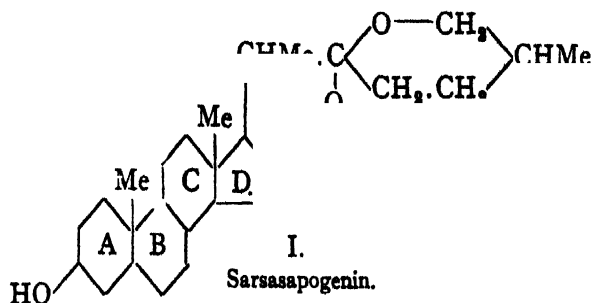
Tigonin, from *D. purpurea* and *D. lanata*, gives tigogenin, glucose (2 mols.), galactose (2 mols.) and xylose.

Sarsasaponin, from *Radix sarsaparilla*, forms sarsasapogenin, glucose (2 mols.) and rhamnose.

It will be noted that the sugars liberated are of the usual types encountered in nature, in which respect the digitalis saponins differ from the accompanying cardiac poisons.

The best investigated saponins are those of the digitalis group. Jacobs and Simpson dehydrogenated gitogenin and sarsasapogenin with selenium and isolated Diels' hydrocarbon ; tigogenin was degraded to ætioallo-bilanic acid, and sarsasapogenin into ætiobilanic acid. When treated with hydrogen chloride in acetic acid (or on selenium dehydrogenation) the sapogenins yield a hexyl methyl ketone, indicating the presence of an 8-carbon group at position 17. The elucidation of the nature of this characteristic group, however, has proved a difficult problem. Work

by Marker and co-workers, however, emphasises the hydrolysis of the side chain in acid media and its stability towards alkali. As a result they advanced the formula I for sarsasapogenin, in which it is represented as having a protected (ketal) carbonyl group. This structure is also in



agreement with the reaction of sarsasapogenin with alkyl magnesium halides to form products containing two esterifiable hydroxyl groups. Sarsasapogenin and tigogenin are both precipitated by digitonin and are therefore classed as (β)-compounds, having the hydroxyl group at C₃ in *cis* position to methyl at C₁₀.

Heterocyclic Compounds¹

REFERENCE has repeatedly been made to the occurrence of cyclic compounds in which the ring systems—unlike those of the carbocyclic series—are composed of other elements in addition to carbon. These are generally classed under the name of **heterocyclic compounds**. Owing to their close relationship to members of the aliphatic series, certain derivatives of this type have already been described in the aliphatic section, *e.g.* ethylene oxide, lactones, cyclic anhydrides, cyanuric acid and purine compounds. These are readily prepared from open-chain compounds, and by rupture of the ring the latter are easily regenerated. The ring systems of the compounds about to be described are distinguished by greater stability, *i.e.*, they are less readily ruptured. Most of such rings resemble the benzene nucleus in containing several unsaturated linkages, and in chemical behaviour the heterocyclic compounds also possess many points in common with those of the benzene series.

Heterocyclic systems are known in great variety, and their study forms one of the most interesting branches of organic chemistry. Only derivatives of ring systems containing carbon in union with the elements oxygen, sulphur and nitrogen will be considered here. Compounds of this type in which sulphur has been replaced by selenium, and others which contain arsenic and phosphorus, have also been prepared. As in the case of carbocyclic compounds, a distinction is again drawn between rings containing three, four, five, six and a still higher number of atoms. The elements which participate with carbon in ring formation are sometimes termed **hetero-atoms**, and according to the number of these present we speak of mono-, di-, or tri-heteroatomic rings, and so on.

It has already been explained (p. 380) that in the carbocyclic series the five- and six-membered types are the most stable. The same generalisation holds true for heterocyclic rings. Heterocyclic compounds containing three- and four-membered rings are relatively unstable, as is shown by the fact that they are difficult to form and readily break up again. Those containing five- and six-membered rings, on the other hand, are usually distinguished by comparatively high stability.

It should also be noted that the number of heterocyclic systems is increased still further by the existence of condensed polynuclear types. Just as naphthalene is composed of two benzene nuclei, and phenanthrene

¹ See also *The Chemistry of Heterocyclic Compounds*, by A. A. Morton (McGraw-Hill), 1946. *Chemistry of Heterocyclic Compounds*, edited by A. Weissberger (Interscience Publishers, London). *Heterocyclic Compounds*, edited by R. C. Elderfield (Chapman and Hall, Ltd., London).

of a benzene and a naphthalene nucleus, so in the same manner benzene, naphthalene and other rings may condense with heterocyclic systems. A complicated example of this kind has already been met with in indanthrene (p. 603), and numerous others will be found in connection with quinoline, indole and their derivatives.

Special importance attaches to those compounds in which a five- or six-membered ring containing nitrogen is present. This class includes the vegetable alkaloids and dye-stuffs such as indigo. Compounds derived from these systems will therefore be treated in greater detail. Five-membered rings containing two or more atoms of nitrogen are frequently named with the ending *azole* (pyrazole, triazole, tetrazole) and six-membered rings with the ending *azine* (pyrazine, triazine, tetrazine).

I

Pyrrole, Furan and Thiophen Groups

The heterocyclic compounds pyrrole, furan, and thiophen (see also pp. 269 and 272), which stand in close relationship to each other, will be described first.

I.—PYRROLE GROUP¹

Among five-membered ring systems containing nitrogen the pyrrol group stands out prominently. Included under this heading are all those chemical compounds, the molecules of which contain a ring built up of four carbon atoms and a nitrogen atom (I)



The pyrrole ring is found in many alkaloids such as nicotine, atropine, etc.; in pyrrolidine-2-carboxylic acid in protein hydrolysates; and especially in hæmoglobin and chlorophyll, thus revealing an interesting connection between the colouring matter of blood and leaves.

The formula now generally accepted for pyrrole (I) as the result of many syntheses of the compound and its derivatives was first advanced by Baeyer. The structural resemblance between pyrrole compounds and those of furan and thiophen is obvious and was clearly demonstrated by the work of L. Knorr and Paal on the formation of these compounds (or their derivatives) from 1 : 4-diketones.

¹ A detailed description of these compounds will be found in a monograph by Hans Fischer and Hans Orth *Die Chemie des Purpurs* (Leipzig 1924)

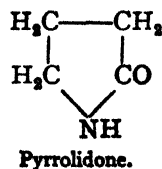
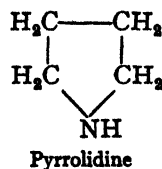
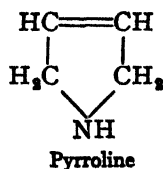
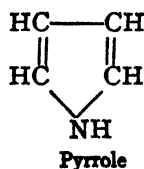
Nomenclature of Pyrrole Derivatives.—The position of substituents in the pyrrole nucleus is usually indicated by the numbers 1 to 5, as in formula I.

Another system makes use of the letters α , β , as in II. Since positions α and α' are equivalent, and also positions β and β' , it is often convenient to distinguish monosubstitution products as α - or β -compounds respectively. Derivatives containing a substituent attached to nitrogen are frequently described as N-compounds.

From the above it is seen that each C-monosubstitution product of pyrrole can exist in two isomerides, as an α - or β -derivative. Each C-disubstitution product can occur in four modifications, viz., as an $\alpha\alpha'$ -, $\alpha\beta$ -, $\alpha\beta'$ - or $\beta\beta'$ -derivative.

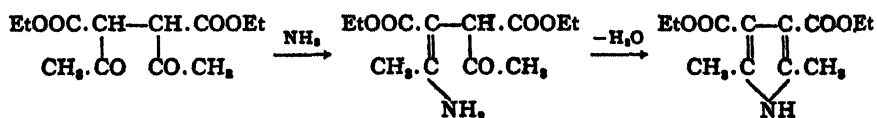
Dihydro-pyrroles are known as **pyrrolines**, and the completely reduced tetrahydro-pyrroles as **pyrrolidines**.

Keto-pyrrolines are termed **pyrrolones**, and keto-pyrrolidines are described as **pyrrolidones**. Distinctions are also drawn between various pyrrolones and pyrrolidones, according to the position and number of keto-groups in the molecule. The term "pyrrolidone" is commonly used to describe 2-keto-pyrrolidine. Substances derived from it can be described either as 2-keto-pyrrolidine or as α -pyrrolidone derivatives, and may be regarded as lactams of γ -amino-acids. The imides of the succinic acid group, of which succinimide itself is the simplest representative, are $\alpha\alpha'$ - or 2 : 5-diketo-pyrrolidines.



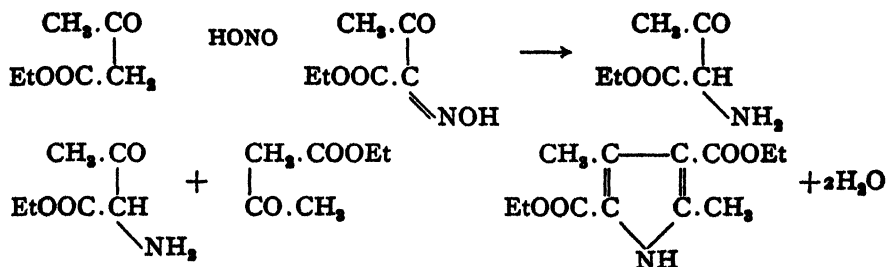
Methods of Forming Pyrrole and Reduced Pyrrole Derivatives

1. The 1 : 4-diketones, when treated with ammonia or primary amines, are transformed with great ease into pyrrole derivatives. This synthesis is effected with equal readiness when the reagents are dissolved in glacial acetic acid, water or ether, and appears to depend on the intermediate formation of amino-ketones (*Knorr*).

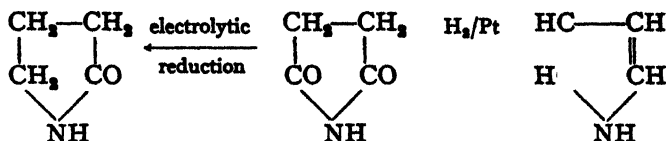


This reaction has proved of service in the preparation of a great number of pyrrole derivatives. Any γ -diketo-compound of the general formula $\text{R} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{R}$ may be employed, and the place of ammonia may be taken by primary amines, amino-acids, hydroxylamine or phenylhydrazine.

2. A second synthesis of pyrrole is also due to L. Knorr, who succeeded in preparing 2 : 4-dimethyl-pyrrole-3 : 5-dicarboxylic ester by reducing an equimolecular mixture of isonitroso-acetoacetic ester and acetoacetic ester by means of zinc dust and glacial acetic acid. In a similar manner other pyrrole derivatives were prepared by reducing mixtures of esters of β -ketonic acids and their isonitroso-compounds.



3. Another method of general applicability is based on the reduction of succinimide to pyrrole by means of zinc dust and acetic acid, or hydrogen and heated platinum sponge (*Bell and Bernthsen*).

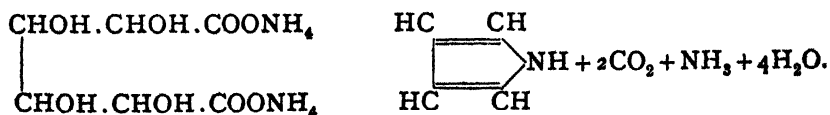


In the same manner pyrroles are formed by the reduction of a variety of acid imides and lactams (which may also be regarded as keto-derivatives of hydrogenated pyrroles).

Different results are obtained by reducing succinimide and its substitution derivatives by electrolytic means (*Tafel*). In this case the corresponding pyrrolidone is formed (formula I), together with very small amounts of pyrrolidine.

Since succinimides are readily prepared in quantity, this process also renders the pyrrolidones easy of access.

4. Pyrrole itself, the parent substance of this class, was first discovered in coal tar and bone tar, and is also present among the distillation products of bituminous shale. It is obtained from the ammonium salt of saccharic acid or mucic acid by heating with glycerol to 200° C.



The use of substituted mucic acids leads to the formation of substituted pyrroles.

I. Compounds of the Pyrrole Series

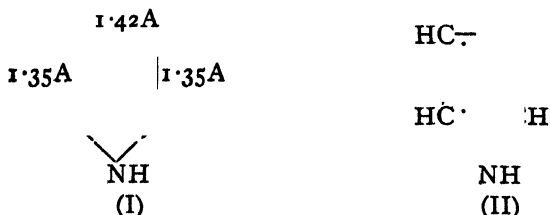
Pyrrole.—The occurrence and formation of pyrrole have already been treated from the general standpoint.

The *preparation of pyrrole* is best effected from bone tar. This is fractionated several times, freed from strongly basic substances by shaking with dilute acid, and again fractionated. Pyrrole distils over in the fraction boiling between 98° and 150° , and may be purified by conversion into the solid potassium compound.

Pyrrole is a colourless liquid which turns brown in air and smells somewhat like chloroform. It boils at 130° to 131° under 761 mm. It dissolves sparingly in water but is readily soluble in alcohol and ether. It is insoluble in aqueous alkalis and only dissolves slowly in acids.

In pyrrole vapour a pine splint moistened with hydrochloric acid is coloured a pale red, which rapidly changes to an intense carmine red. It was by this reaction, now employed as a test for pyrrole, that the compound was first detected in 1834 by Runge.

Pyrrole is a resonance hybrid with the classical structure (I) as the main contributing form. This is supported by the lengths of the C_2-C_3 and C_4-C_5 bonds having a smaller value than the others. The two

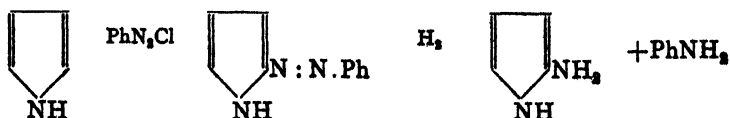


electrons from the nitrogen atom are required to complete the aromatic sextet of electrons (II) and hence are not available to combine with a proton. Pyrrole is therefore a very weak base, which dissolves slowly in dilute acids. With strong acids it is rapidly resinified. Even from solutions in dilute acids it is only possible to isolate definite simple salts in a few cases, and resinification readily takes place. This action of acids on pyrrole is probably due to polymerisation.

Many of the reactions of pyrrole are similar to those of phenols, while others resemble those of the aromatic amines. Some reactions again are due to the presence of the two conjugated double bonds, while others are simply characteristic of the pyrrole molecule.

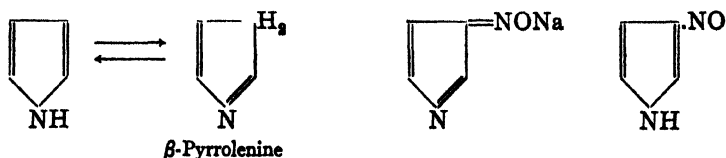
Phenolic properties.—The analogy with phenols is shown by the similarity in behaviour of the :NH group in pyrrole with that of the phenolic hydroxyl group. Potassium and pyrrole, for example, react with evolution of hydrogen and formation of the solid *potassium pyrrole*, C_4H_4NK . Pyrroles, like phenols, readily couple with diazonium salts to give azo-compounds. The azo-group assumes an α -position, or if both of these are occupied, a β -position. Thus pyrrole and benzene diazonium chloride yield *pyrrole-azobenzene* and *pyrrole-disazobenzene*.

The former on reduction with zinc and hydrochloric acid gives aniline and 2-aminopyrrole, which is best prepared by this method.

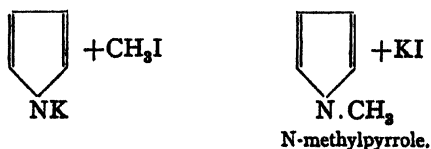


Like phenol (and aniline) pyrrole is very readily substituted by halogens, the four methine hydrogen atoms being replaceable. So facile is the substitution, that tetraiodopyrrole or *Iodole* is formed directly from pyrrole and iodine in indifferent solvents. It is an antiseptic similar to iodoform, but is odourless and less toxic.

The nitroso-pyrroles exhibit tautomeric phenomena similar to those shown by the nitroso-phenols. With nitrous acid (generated by the action of sodium ethylate on amyl nitrite) pyrrole forms the sodium salt of 3-isonitroso-pyrrole, which with hydrochloric acid gives 3-nitroso-pyrrole. In this reaction pyrrole acts in the β -pyrrolenine form.

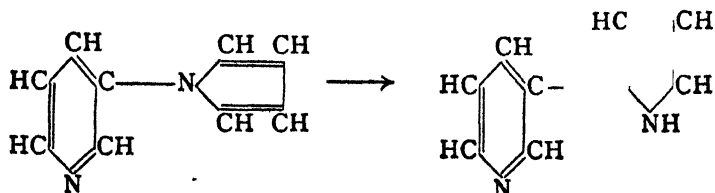


Finally, *N*-substituted pyrroles are prepared from potassium pyrrole, e.g.



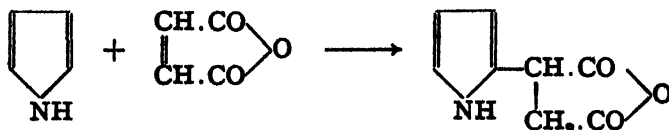
Comparison with Aromatic Amines.—*N*-substituted anilines under certain conditions are converted into primary amines through a migration of a substituent from nitrogen to carbon. In the same way the *N*-alkyl or acyl derivatives of pyrrole are transformed by heat into *C*-derivatives.

Pictet and Crepieux, for example, by distilling *N*-pyridyl-pyrrole through a tube at low red heat converted it into *C*-pyridyl-pyrrole.

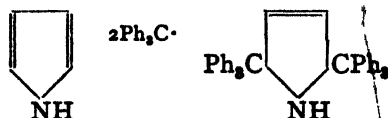


This conversion formed one of the stages of Pictet's synthesis of nicotine.

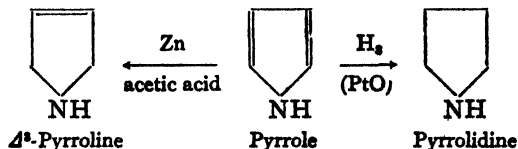
Diene Properties.—Conjugated double bonds in organic compounds are detected by the Diels-Alder reaction, but this method cannot be applied to pyrrole, since pyrrole with maleic anhydride does not give the typical condensation but instead forms 2-pyrrole-succinic anhydride.



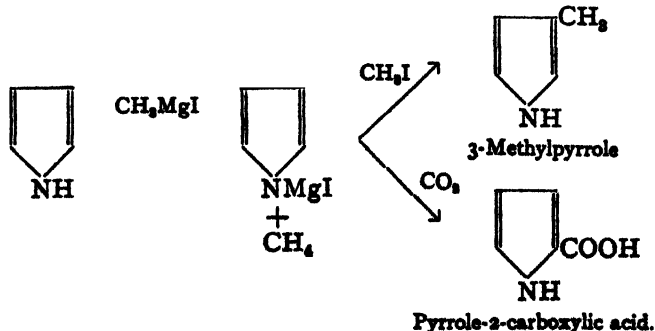
The diene system, however, may be detected by the triphenylmethyl radical, two molecules of which are known to add on to the terminal carbon atoms of two conjugated double bonds to give bis-triphenylmethyl derivatives (see p. 125). This reagent was shown by Conant and Chow¹ to yield with pyrrole 2 : 5-bis(triphenylmethyl)-pyrrole.



The double bonds are also shown by reduction, zinc and acetic acid yielding Δ^2 -pyrroline (1 : 4 addition), and hydrogen with platinum oxide catalyst **pyrrolidine** (tetrahydropyrrole) see p. 662.

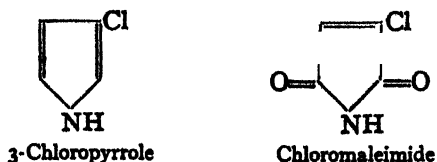


Other Reactions.—The α -position is the more reactive in pyrrole. Substitution, however, does not occur exclusively in the α -position, and frequently smaller quantities of β -derivatives are obtained as by-products. Occasionally the reverse occurs; for example, methylmagnesium iodide reacts to form N-pyrrolylmagnesium iodide, which when treated with methyl iodide gives 3-methylpyrrole and a little of the 2-isomer. Groups other than the methyl enter the 2- or 5-position unless both are blocked. Thus carbon dioxide yields pyrrole-2-carboxylic acid.



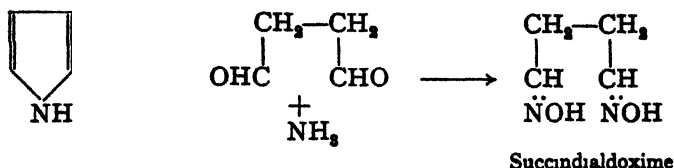
¹ Conant and Chow, *J.A.C.S.*, 1935, 55, 3475.

Oxidation with chromic oxide and sulphuric acid readily converts pyrrole derivatives into the corresponding imides of maleic acid, *e.g.*



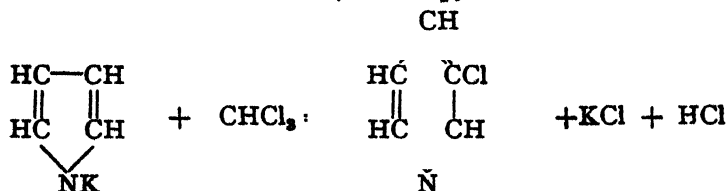
This oxidation is a valuable means of determining the orientation of substituents in the pyrrole nucleus and also for detecting the presence of a pyrrole ring in substances of unknown constitution. For example, the pyrrole nature of hæmatin was demonstrated by oxidising the latter to a compound which proved to be a substituted imide of maleic acid. Another example is the oxidation of tropinic acid to *N*-methylsuccinimide (p. 753).

The pyrrole ring was shown by Ciamician to be opened by alkali and if the reaction is carried out in presence of hydroxylamine succindialdoxime is formed.



Other methods of ring-opening are discussed on p. 663.

From the phenolic character of pyrrole it might be expected that pyrrole with chloroform and aqueous alkali will give a pyrrole aldehyde, *cf.* p. 522. This is indeed the case; but the pyrrole ring is transformed into the pyridine ring when pyrrole or potassium pyrrole is heated with sodium ethoxide and chloroform: *β*-chloro-pyridine is formed.



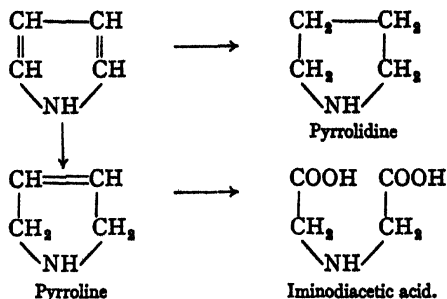
This is a general reaction for pyrrole, and is also given by its homologues and the indoles (p. 673).

2. Hydropyrrole Derivatives

Hydropyrroles are obtained by direct hydrogenation of pyrrole derivatives; by the degradation of alkaloids; and by synthesis from aliphatic compounds.

The reduction of pyrrole compounds to di- and especially to tetrahydroderivatives offers considerable experimental difficulty; in this respect these compounds differ from the pyridine group. Reduction with

hydriodic acid or by hydrogen in presence of a catalyst yields pyrrolidine, while zinc dust and acetic acid give pyrroline, the structure of which was proved by ozonisation to iminodiacetic acid.



Addition of hydrogen brings about a decided change in chemical nature. Whereas pyrrole itself is a weak base, pyrroline and to a still higher degree pyrrolidine possess the strong basic properties of the secondary aliphatic amines. This is the usual consequence of hydrogenating an aromatic system, as has already been seen in the case of the naphthylamines and will be observed again in the pyridine group.

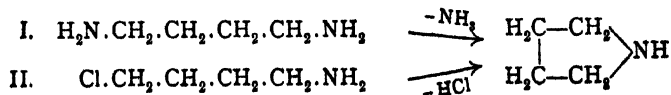
Pyrrolidine and its derivatives present a striking resemblance to the corresponding compounds of the piperidine series. This similarity extends even to physical properties and is best illustrated by comparison with the analogy existing between compounds of the pentamethylene and hexamethylene groups.

The discovery of pyrrolidine in 1885 was followed immediately by the recognition of its resemblance to piperidine and its description as a lower nuclear homologue of the latter (*Ciamician*).

Pyrrolidine, tetrahydro-pyrrole, $\text{C}_4\text{H}_8\text{NH}$, may be obtained by the following methods :—

1. It was first prepared by heating pyrrole with hydriodic acid and phosphonium iodide at 240° to 250° . Obviously the less hydrogenated compound pyrroline must be formed as an intermediate product, and this can also be used as starting material.

2. It can also be prepared by distillation of the hydrochloride of tetramethylene diamine (I) or by the interaction of δ -chlorobutylamine (II) and sodium hydroxide.

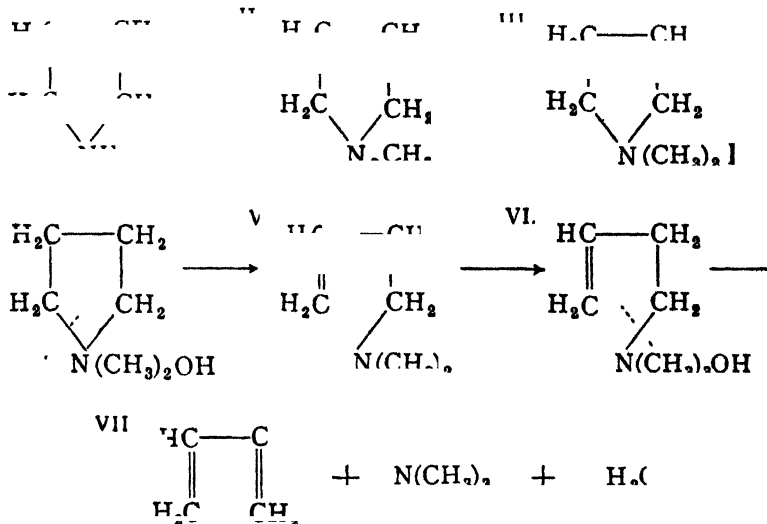


Despite the variety of preparative methods available pyrrolidine is a difficultly accessible compound. It is a strongly alkaline liquid of boiling-point 86° to 88° ; it is miscible with water and possesses a pungent ammoniacal smell recalling that of piperidine. In general it shows great similarity to piperidine.

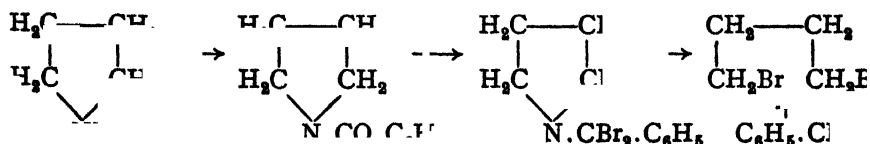
Behaviour of Pyrrolidine on Exhaustive Methylation, etc.—

The opening of the pyrrolidine ring has already been mentioned. There are, however, other methods of much wider application which break the nitrogen-carbon bonds in reduced heterocyclic compounds containing five- or six-membered rings. Two of these methods may be mentioned. Further details may be found on p. 722.

Exhaustive Methylation.—If dimethylpyrrolidinium iodide (III) is heated with caustic potash a decomposition ensues resembling that described below under dimethyl-piperidium hydroxide. Under these conditions the ring opens with formation of an unsaturated aliphatic base, Δ^3 -butenyl-dimethylamine (V) (incorrectly called dimethylpyrrolidine). The methiodide of this base, on distillation with alkali, yields trimethylamine and butadiene (VII)

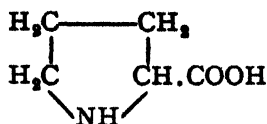


von Braun's Method.—N-Benzoylpyrrolidine when treated with phosphorus pentabromide yields benzonitrile and 1:4-dibromo-n-butane. The method is not only valuable for determining the structure of pyrrol derivatives, but affords an excellent method of preparing aliphatic dibromides.

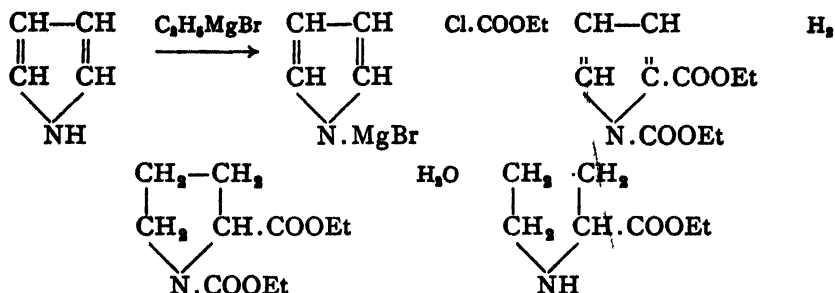
**3. Pyrrolidine Carboxylic Acids.**

Considerable attention has been devoted to the pyrrolidine carboxylic acids since their presence in the degradation of the *coca* and *atrop* alkaloids and in the hydrolysis products of casein, egg albumin, blood fibrin etc. was established.

Pyrrolidine-2-carboxylic acid, *proline*, is a primary hydrolysis product of proteins.

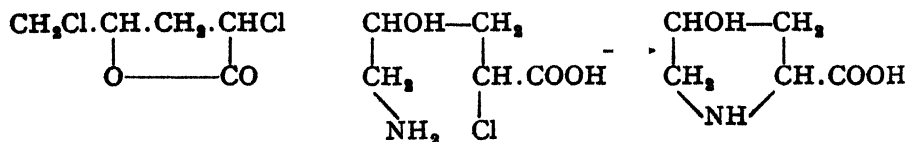


Proline may be prepared synthetically or by the hydrogenation of pyrrole-2-carboxylic acid or its derivatives (see p. 660). Probably the best method is that of Signaigo and Adkins¹ in which 1 : 2-dicarbethoxypyrrole is hydrogenated under pressure in presence of a nickel catalyst.

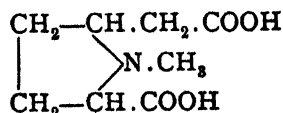


After careful drying, *pyrrolidine-2-carboxylic acid* melts with gas evolution at 205°. In aqueous solution it gives a weakly acid reaction with litmus, and possesses a sweet taste. For the separation and identification of the acid the *copper salt* is of service, and has frequently been used for identifying the compound obtained from proteins.

β -Hydroxypyrrolidine- α -carboxylic acid, *hydroxyproline*, occurs in animal protein, rarely in vegetable protein. Its structure was shown by the formation of proline on reduction with phosphorus and hydriodic acid and synthesis from $\alpha\delta$ -dichloro-valerolactone and ammonia: this second reaction establishes the position of the hydroxyl group.



Tropinic acid, 1-methyl-pyrrolidine-2-carboxy-5-acetic acid

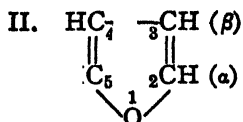
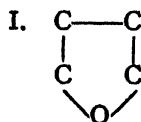


When tropine and ecgonine (see chapter on Alkaloids) are oxidised with chromic acid they yield dicarboxylic compounds, $\text{C}_8\text{H}_{13}\text{NO}_4$,

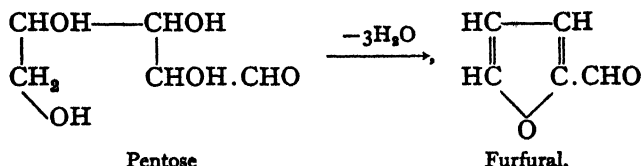
¹ *J.A.C.S.*, 1936, 58, 1122.

FURAN GROUP¹

Furan, as indicated on p. 269, is closely related to pyrrole, but is less important. It contains a ring composed of four carbon atoms and one oxygen atom (I). The ring is numbered as in (II).

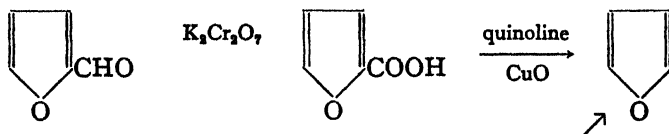


The synthesis of furan derivatives by elimination of water from γ -diketo-compounds has already been described (see pp. 269 and 272), and affords a good illustration of the close relationship between pyrrole and furan. A second method and one which is used on the commercial scale is by heating certain carbohydrates with mineral acids. **Furfural**, α -furaldehyde, is obtained industrially by heating oat-hulls with moderately concentrated sulphuric acid (see p. 303), the *pentosans* present being hydrolysed to pentoses which in turn lose the elements of water to yield the aldehyde.



Furfural, b.p. 162° , is a colourless oil of pleasant smell and is used on the large scale as a solvent for purifying lubricating oils and for the manufacture of resins similar to "Bakelites" by condensation with phenols in the presence of suitable catalysts. It is detected by the formation of an intensely red dye-stuff when heated with aniline and hydrochloric acid.

Furfural is obviously a valuable substance for the preparation of other α -substituted furan derivatives. For example, it yields with potassium dichromate **α -furoic acid** (pyromucic acid, α -furan-carboxylic acid), m.p. 134° , which is readily decarboxylated on heating with quinoline and copper oxide to give furan (see also p. 667).

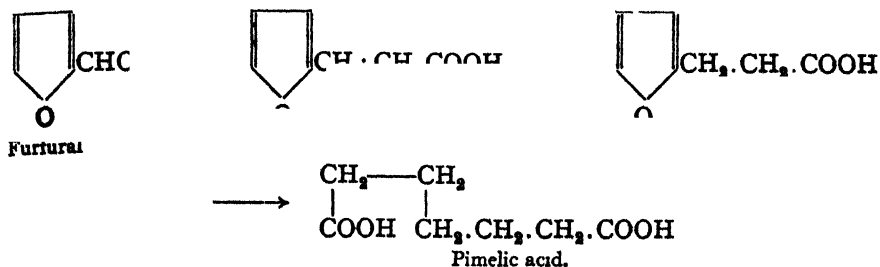


Furan is obtained commercially by heating furfural at 400° in presence of a catalyst, carbon monoxide being eliminated.

Furfural is a "key" compound for the orientation of α -furan derivatives. It was shown to be an α - and not a β -derivative by heating

¹ See also L. N. Owen, *Ann. Reports*, 1945, 42, 157. D. G. Jones and A. W. C. Taylor, *Quart. Reviews*, 1950, 4, 195.

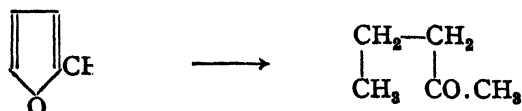
it with acetic anhydride and sodium acetate (*Perkin reaction*) to give furyl-acrylic acid, which by successive reduction, ring-opening, oxidation,



and reduction gave pimelic acid. Had the aldehyde group been in the β -position a branched-chain dibasic acid would have resulted.

α -Derivatives are much more readily obtained than β -, partly because there is no compound in the β -series so accessible as furfural, but chiefly because substitution invariably occurs in the α -position, unless both are already occupied. β -Derivatives are therefore prepared from 2:5-disubstituted furans followed by the removal of the α -groups.

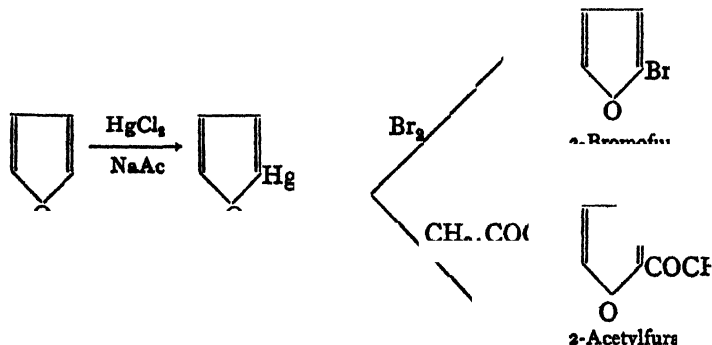
The furan ring can be opened by hydrogenation under controlled conditions with copper, nickel, or platinum catalysts. Thus 2-methylfuran with Raney nickel at 185° yields pentan-2-one.



Furan and its derivatives possess a dual set of properties. They behave on the one hand as aromatic substances and on the other as diene ethers.

Aromatic Properties.—Furan undergoes substitution more readily than benzene, and is somewhat exuberantly described by American workers as possessing "super-aromatic" properties. It is very readily acylated not only with aluminium chloride but also with milder reagents such as zinc and stannic chlorides. The enhanced reactivity of the furan nucleus is shown by the fact that in these reactions benzene may be used as solvent.

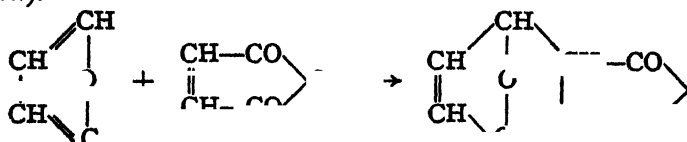
Furan very readily undergoes mercuration with mercuric chloride and



sodium acetate and the *α*-chloromercurifuran so obtained is useful for the preparation of *α*-substituted furans.

Halogenation, nitration, and sulphonation are best carried out on substituted furans containing benzoyl or carboxyl groups, which prevent tar formation.

Diene Properties.—The conjugated bonds in the furan ring are shown by condensation of furan with maleic anhydride, etc. (*Diels-Alder reaction*).



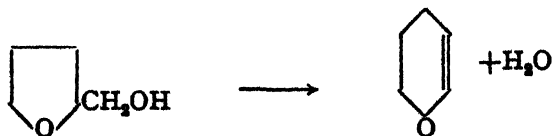
Furan is also readily reduced to *tetrahydrofuran* with hydrogen and a palladium catalyst at moderate temperatures and pressures.

A striking example of the aromatic properties of furan derivative is furnished by furfural which in its chemical character is aromatic in type and a complete analogue of benzaldehyde. Like all aldehyde it forms an oxime and a hydrazone, and in addition undergoes a series of reactions in which the resemblance to benzaldehyde is clearly visible. Thus with alcoholic potassium cyanide it yields *furoin* ($\text{C}_4\text{H}_5\text{O} \cdot \text{CHOH} \cdot \text{CO} \cdot \text{C}_4\text{H}_5\text{O}$), an analogue of benzoin; with sodium acetate and acetic anhydride it is converted into *furyl-acrylic acid* ($\text{C}_4\text{H}_5\text{O} \cdot \text{CH} : \text{CH} \cdot \text{COOH}$) (compare cinnamic acid by *Perkin's reaction*). It also undergoes the *Cannizzaro* reaction to give *furyl alcohol* and *furoic acid*.

On the other hand, no hydroxy-furans with phenolic properties are known, and the amino-furans in sharp contrast to aniline are not easily prepared, are not very stable, and are not readily diazotised. The resulting diazo solutions, moreover, though coupling with *α*-naphthol do not show the typical diazo reactions.

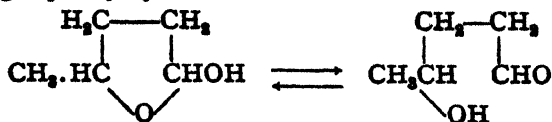
α-Furoic acid is another example of a "non-aromatic" furan derivative. It might be expected to behave as an analogue of benzoic acid, but its reactions give no indication of aromatic character and place it rather with the unsaturated aliphatic acids. It immediately decolorises an alkaline solution of potassium permanganate and when exposed to bromine vapour takes up four atoms of bromine.

Tetrahydrofurfuryl alcohol, obtained by the catalytic reduction of



furfural, is a valuable commercial solvent. It is used to prepare 2:3 dihydropyran by catalytic dehydration and accompanying ring-expansion.

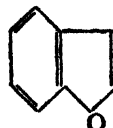
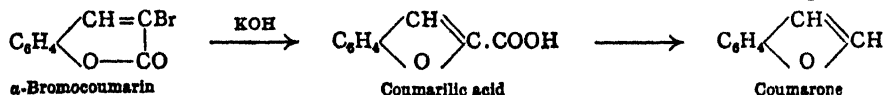
Some hydrogenated furans exhibit ring-chain tautomerism. 2-Hydroxy-5-methyltetrahydrofuran, for example, behaves both as a cyclic ether by forming a cyclic methyl ether, and as γ -hydroxyvaleraldehyde by yielding a phenylhydrazone.



Coumarone or Benzofuran Series

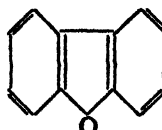
Compounds of this class contain a benzene and a furan nucleus condensed together with two carbon atoms in common. The parent substance of the group, coumarone, thus bears the same relationship to naphthalene as furan to benzene. To furan it is related in the same way as indole (see later) to pyrrole.

Coumarone derivatives take their name from their formation by the action of alcoholic potash on α -halogen-substituted coumarins, as a result of which a six-membered ring is converted into a five-membered ring :



Coumarone.

Coumarone can be prepared by other methods in addition to those described above, and is also found together with a number of methyl coumarones in coal tar. It boils at 169° to 170°, and is an extremely stable, indifferent compound. Strong mineral acids bring about resinification and formation of a polymeride known as *paracoumarone*. On leading a mixture of coumarone and benzene (or naphthalene) in the vaporous state through a heated tube, phenanthrene (or chrysene, see p. 616) is formed.



Diphenylene oxide.

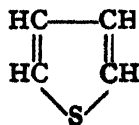
With chlorine and bromine coumarone yields dihalogen addition products, which, on being treated with alcoholic potash, give chloro- and bromo-coumarones. Nitro-derivatives are also known. A large number of derivatives containing alkyl groups in the benzene and furan nuclei have been prepared by synthesis.

Diphenylene oxide may be regarded as *dibenzo-furan*. It forms white leaflets, m.p. 81°, b.p. 288°, and is found in coal tar. It is prepared by distilling phenol with lead oxide.

III. THIOPHEN GROUP ¹

Whereas pyrrole, as already emphasised, shows a strong resemblance to the phenols, thiophen possesses many points in common with benzene. This similarity extends also to derivatives of the two compounds.

Thiophen is present to about 0.5 per cent. in coal-tar benzene, in which it was detected in 1882 by Victor Meyer, who a year later obtained sufficient to analyse it and determine its properties. Homologues of thiophen are present in the benzene homologues prepared from coal-tar; thus both α - and β -methylthiophens or *thiotolenes* are contained in commercial toluene. This is explained by the fact that corresponding derivatives of the benzene and thiophen series possess approximately the same boiling-points.



¹ F. F. Blicke, *The Chemistry of Thiophen (Heterocyclic Compounds)*, edited by R. C. Elderfield, Vol. I, p. 208.

Boiling-points

Thiophen	84.0° C.	Benzene	80.09° C
Methylthiophen	113.0° C.	Toluene	110.3° C.
Ethylthiophen	132.4° C.	Ethylbenzene	136.2° C.
Chlorothiophen	130.0° C.	Chlorobenzene	132.0° C.
Benzoylthiophen	326.0° C.	Benzophenone	306.0° C.

Thiophen can be extracted from commercial benzene by repeated shaking with small quantities of concentrated sulphuric acid, and decomposing the thiophen sulphonic acid so obtained by heating it strongly with water. This method of separation is by no means ideal, since either some benzene is simultaneously sulphonated, or, by using smaller amounts of sulphuric acid, the thiophen is only incompletely removed.

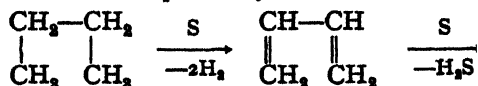
A better and quantitative method of isolating thiophen from commercial benzene was developed by O. Dimroth. This consists in heating the mixture to the boiling-point with a solution of mercuric acetate, when thiophen is attacked with the formation of *thiophen-aa'-dimercuri-hydroxyacetate*, $\text{HOHg} \cdot \text{C}_4\text{H}_2\text{S} \cdot \text{HgOOC} \cdot \text{CH}_3$. The latter separates out as a solid, whereas the less reactive benzene is not attacked at this temperature. On distilling the mercury compound with moderately concentrated hydrochloric acid it readily decomposes into mercuric chloride and thiophen. This method enables thiophen to be isolated in the pure state without loss of either thiophen or benzene.

The best and quickest method, however, is to shake the impure benzene with Raney nickel. Thiophen-free benzene is thus obtained in a few minutes.

Thiophen may be obtained by heating sodium succinate with phosphorus trisulphide. This is an isolated example of a general method for preparing thiophen and its substituted products from 1:4-dienols (see pp. 269, 272).



Thiophen derivatives can also be prepared from saturated or unsaturated hydrocarbons and sulphur at a high temperature. Thiophen, for example, is now manufactured in the United States by heating *n*-butane with sulphur, which acts both as dehydrogenating and cyclising agent. The mechanism is probably as follows:—



S

Thiophen resembles benzene not only in its physical but also in its chemical properties. It is more reactive than benzene but less than furan. The α - is the reactive position though substitution, in contrast to that of furan, does not occur there exclusively.

Bromination of thiophen in glacial acetic acid or benzene proceeds

energetically to give 2:5-dibromothiophen, while milder reagents and conditions are required for monobromothiophen.

Benzoylation and acylation occur very readily with aluminium chloride or even with phosphorus pentoxide.

α -Thiophen aldehyde is not so accessible as furfural, the corresponding furan aldehyde, but behaves like an aromatic aldehyde giving the *Perkin* and *Cannizzaro reactions*, etc.

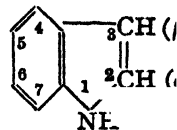
It should be noted, however, that not all the properties of thiophen derivatives can be described as aromatic. *2-Amino-thiophen*, for example, obtained by reduction of *2-nitrothiophen* with tin and hydrochloric acid, is unstable in air and does not form diazonium compounds with nitrous acid. Hydroxythiophens are unknown.

The diene character of thiophen is not so marked as that of furan. Thiophen, for example, does not react with maleic anhydride.

II

Indole Group¹

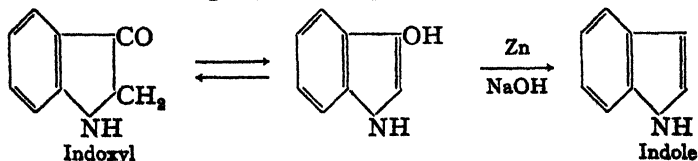
The molecule of indole contains a benzene nucleus condensed with a pyrrole nucleus, as in the annexed formula. As the parent substance of indigo it possesses an outstanding interest: indeed it was in the course of the investigation on the constitution and synthesis of indigo that Baeyer prepared indole and its derivatives and studied their properties. Indole and substituted indoles are also important from the biochemical point of view, owing to their occurrence as disruption products of proteins. Four compounds of this group have long been known to be present among the putrefaction products of proteins, namely, indole itself, skatole, skatole-carboxylic acid, and tryptophan.



Indole, C_8H_7N , is produced in small amounts by the putrefaction of albuminous material, and is present in fæces; it is also formed by the alkaline hydrolysis of proteins. It occurs in coal tar, and has been isolated from a fraction of tar oil, boiling between 240° and 260° . Indole is also present in jasmine-flower oil ($2\frac{1}{2}$ per cent.), in orange blossom and other flowers. The structural formula quoted above was advanced by Baeyer before the compound itself had been discovered.

Indole is obtained by the following reactions:—

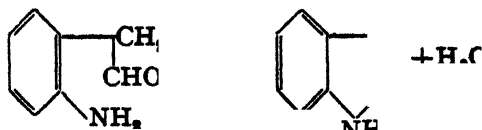
1. From its oxygenated derivatives, such as indigo, oxindole, or indoxyl, by reduction: e.g. by reducing indoxyl with zinc dust and alkali.



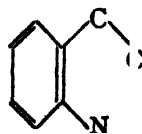
It was first prepared by the reduction of indigo.

¹ R. B. Van Order and H. G. Lindwall, *Chem. Rev.*, 1942, 30, 69.

2. By the internal condensation of various *o*-substitution products of aniline (or of nitrobenzene, after preliminary reduction); e.g. by elimination of water from *o*-aminophenylacetaldehyde.



Indole is obtained by a number of similar syntheses, the substances used being nitrobenzene or aniline with a two carbon side-chain in the *ortho* position. The structure of indole follows from these syntheses.

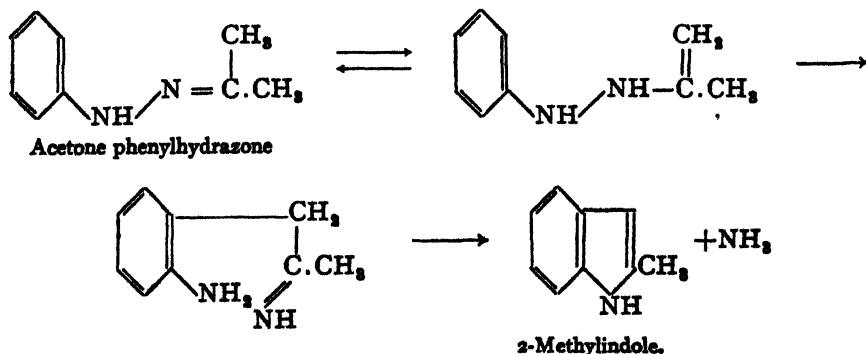


Indole crystallises in plates, m.p. 52° and b.p. 245° (with partial decomposition). It is volatile in steam, and in the ordinary state possesses an unpleasant faecal odour. After very careful purification, however, indole may be mixed in suitable dilution with other perfumes, with the surprising result that the odour of fresh flowers is imparted to the mixture. The presence of indole in jasmine-flower oil is therefore a very important factor in producing the specific perfume of jasmine.

Substituted indoles occur in coal tar, and may be prepared from the higher fraction, b.p. 250° to 275° , of the technical crude indole.

Two valuable synthetic methods are :—

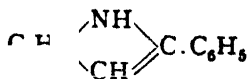
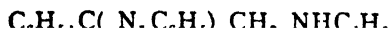
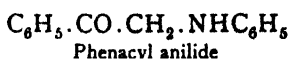
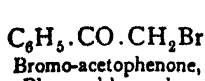
1. *Fischer Indole Synthesis*.—Substituted indoles are obtained in good yield by heating the phenylhydrazones of certain aldehydes and ketones with zinc chloride, sulphuric acid, etc. The mechanism of this remarkable reaction has been the subject of controversy. The most plausible theory is that of Robinson¹ in which an *o*-benzidine rearrangement is assumed to occur.



This is the most general method for the preparation of substituted indoles.

¹ R and G. M. Robinson, *J.*, 1918, 122, 630; *J.*, 1924, 122, 827.

2. By the action of substituted anilines on anilides of ketones or aldehydes of the general formula $R'.CO.CH(NHC_6H_5).R''$. Anilides

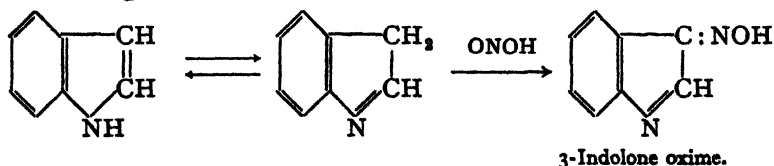


α -Phenyl-indole.

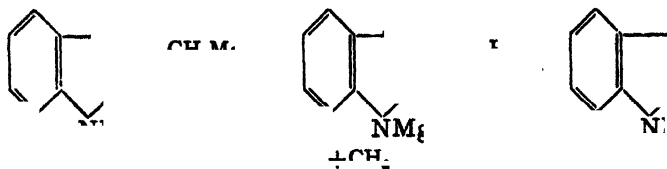
of this type may be prepared from halogen derivatives of ketones and aldehydes, in which halogen is attached to the carbon atom adjacent to the carbonyl group, *i.e.*, from compounds containing the group $-CO.CHCl-$.

The reactions of indole and its simple substitution derivatives resemble those of pyrrole, modified by the annealed benzene ring. Indole, like pyrrole, possesses weakly basic and at the same time somewhat phenolic properties. Similarly, it is easily resinified with acids, and gives a cherry-red colour to a pine splint moistened with hydrochloric acid. It forms the sodium derivative, *sodium indole*, with sodium or sodamide. Substitution in the pyrrole nucleus occurs so strongly that unless mild reagents are used unworkable resinous products result. 3-Chlorindole, for example, is prepared by the action of sulphuryl chloride: chlorine forms a tar.

Like pyrrole, indole resembles the phenols in some respects. With chloroform and alkali it gives *indole-3-aldehyde* and 3-chloroquinoline, the latter by *ring-enlargement*. Diazonium compounds give 3-azo-derivatives, and nitrous acid 3-isonitroso-indole (3-indolone oxime), the indole reacting in the tautomeric *indolenine* form.



It is obvious that the reactive position in indole is position-3. Other examples of this are acetylation which gives 1-acetyl- and 1:3-diacetyl indole, and the formation of 3-alkyl-indoles by the action of alkyl halide on *indolylmagnesium iodide*



Reduction of indole by hydrogen and a platinum catalyst gives 2:3-dihydroindole. Mild oxidation gives indigo, and stronger oxidatic

(*e.g.* potassium permanganate and acetic acid) of the *N*-benzoyl-derivative gives benzoyl-anthranilic acid. This is of value in structural determinations. For example, the constitution of 5-nitroindole is shown by its oxidation to 5-nitro-*N*-benzoyl-anthranilic acid.



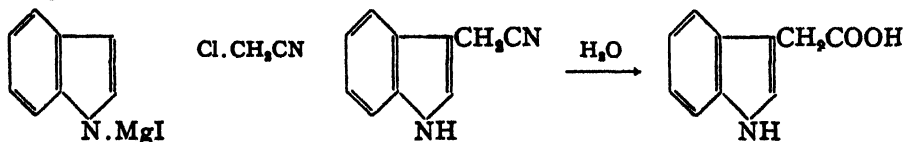
2-Methylindole (m.p. 59°, b.p. 272°) is obtained from acetone phenylhydrazone by the Fischer method. Its structure is established by oxidation with perbenzoic acid to the acetyl derivative of *o*-aminobenzaldehyde.¹

3-Methylindole, skatole, (m.p. 95°, b.p. 268°), is the best-known homologue of indole. It is found in nature along with indole, and is present in human faeces. It is synthesised from propionaldehyde phenylhydrazone.

Indole-carboxylic Acids.—Many of the acids have been prepared by Fischer's method (already described) in which the phenylhydrazones of ketonic or aldehydic acids, such as pyruvic or lævulinic acid are heated with zinc chloride. Other methods, however, are sometimes advantageously employed.

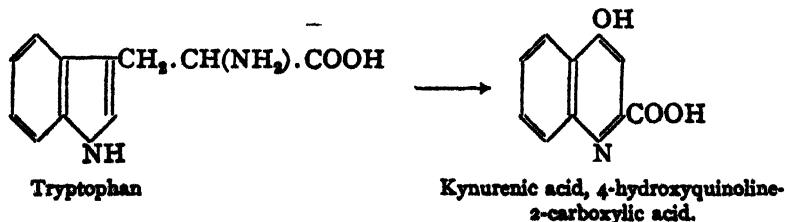
The acids are solid, odourless substances with distinctly acidic and very little basic character. They easily decompose into carbon dioxide and derivatives of indole.

Indole-3-acetic Acid, Heteroauxin, m.p. 164°, is formed during the decomposition of proteins and is conveniently synthesised by the hydrolysis of indole-3-acetonitrile, formed by interaction of indolyl-magnesium iodide and chloroacetonitrile. It loses carbon dioxide to form



skatole when heated above its melting-point. It is a plant hormone (see p. 859).

Tryptophan is the compound which gives rise to all the derivatives of indole formed during the putrefaction of proteins. It occurs in most



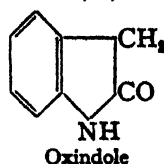
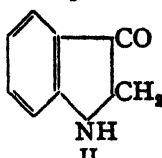
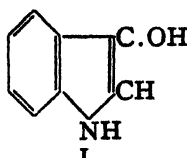
¹ B. Witkop and H. Fiedker, *Ann.*, 1947, 558, 91.

proteins but not in gelatin and zein and can be synthesised from indole.¹ In the organism of the dog it is converted into kynurenic acid, whose structure follows from synthesis and from two reactions: (1) decarboxylation to 4-hydroxyquinoline and (2) replacement of the hydroxyl group by hydrogen to yield quinaldinic acid.

The Hydroxy-Indoles

Indoxyl, is present in the form of the potassium salt of indoxylsulphuric acid in the urine of mammals and as the glucoside in indican. In alkaline solution it is readily oxidised, even by the oxygen of the air, to give indigo. It is an intermediate in the preparation of indigo by the phenylglycine process (see p. 680).

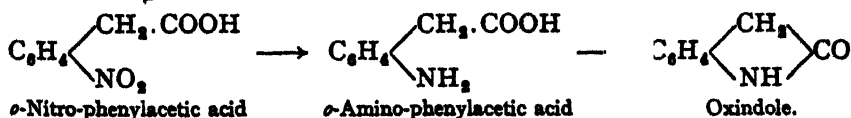
Indoxyl is best prepared by fusing phenylglycine with sodamide (see p. 681), and its structure follows from this synthesis as well as from others, from its reduction to indole with sodium amalgam, and its oxidation to isatin with manganese dioxide and caustic soda. It is a tautomeric substance which behaves as if it had a phenolic (I) or ketonic (II) structure.



The former is the stable form, while the reverse holds for the isomeric substance oxindole. As a hydroxy compound it forms an ester with sulphuric acid, indoxylsulphuric acid, and an *o*-acetyl compound with acetic anhydride and aqueous alkali.

Indoxylic Acid, m.p. 122°-123°, is of importance since it occurs as an intermediate product in the technical synthesis of indigo from phenylglycine-*o*-carboxylic acid. It readily breaks up into carbon dioxide and indoxyl; with oxidising agents it yields indigotin.

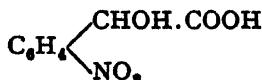
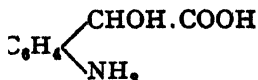
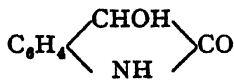
Oxindole is the lactam or inner anhydride of *o*-amino-phenylacetic acid. It is produced by reducing either *o*-nitro-phenylacetic acid or dioxindole with tin and hydrochloric acid, or by reducing isatin with sodium amalgam.



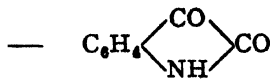
Oxindole crystallises in colourless needles, m.p. 120°, and possesses basic as well as acidic character, being soluble in both acids and alkalis. The action of alkalis at higher temperatures ruptures the indole ring to form salts of *o*-amino-phenylacetic acid. Oxidising agents convert it first into dioxindole.

¹ H. R. Snyder and C. W. Smith, *J.A.C.S.*, 1944, 66, 350. N. F. Albertson, S. Archer and C. M. Suter, *ibid.*, 500.

Dioxindole is the lactam of *o*-amino-mandelic acid, and is formed in an analogous manner to oxindole by reduction of *o*-nitro-mandelic acid with zinc dust and acetic acid, and also by reduction of isatin. It crystallises in colourless prisms, m.p. 180°. On oxidation it yields isatin, and on reduction oxindole.

*o*-Nitro-mandelic acid*o*-Amino-mandelic acid.

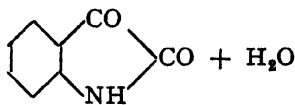
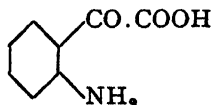
Dioxindole



Isatin.

Isatin crystallises in orange-red prisms, m.p. 200°-201°, and was first obtained by the oxidation of indigo with chromic acid. It can also be obtained by the oxidation of hydroxyindoles such as indoxyl. It is best prepared by cyclisation of isonitrosoacetanilide with sulphuric acid.

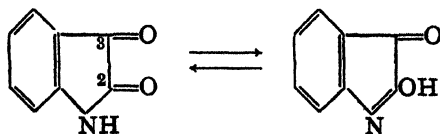
The structure of isatin is shown by its preparation from *o*-aminobenzoylformic acid by elimination of water. The constitution is that of



Isatin.

an inner anhydride of *o*-aminobenzoylformic acid. When fused with caustic alkali isatin yields aniline, and with dilute nitric acid it is oxidised to nitrosalicylic acid. It is therefore concluded that the substance contains a nitrogen and a carbon atom in direct union with the benzene nucleus. Baeyer's investigation of the reduction products of isatin—dioxindole, oxindole, and indole—finally led to the constitution of the compound being established, and to the acceptance of the above formula which had been proposed as early as 1869 by Kekulé.

Isatin presents one of the oldest examples of tautomerism, and reacts in the *lactam* form (I) or *lactim* form (II). Only in a few reactions does

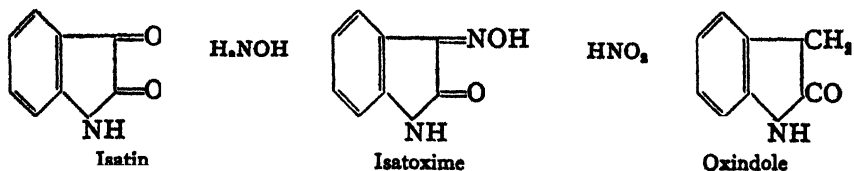


Isatin

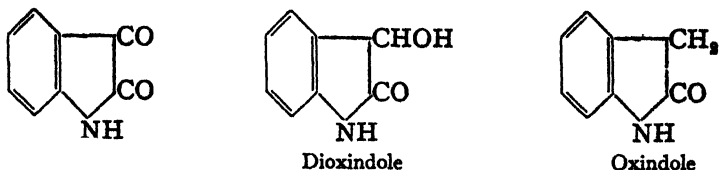
II

isatin react as a diketone, the 2-carbonyl group being part of an amide structure and consequently having the carbonyl properties well masked. The carbonyl group at C₃ is readily revealed by the usual reactions. Isatin unites with sodium bisulphite, and gives a phenylhydrazone with phenylhydrazine. With hydroxylamine it yields *isatoxime*, which is

identical with the *iso*-nitrosooxindole obtained by the interaction of oxindole with nitrous acid. The reactivity of the C₃-carbonyl group is

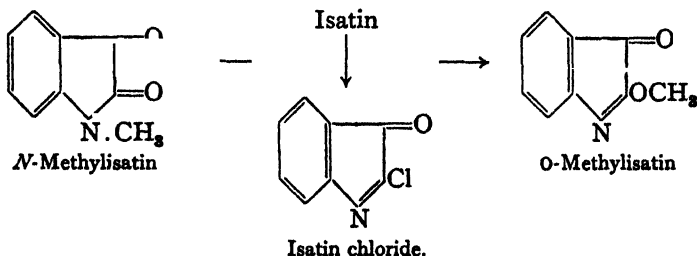


also reflected in the reduction of isatin with zinc and hydrochloric acid to give dioxindole or oxindole according to the strength of the acid used.



As a lactam, isatin readily undergoes ring fission with warm alkali with the production of *o*-aminobenzoylformic acid.

The tautomerism of isatin has been clearly demonstrated. The nitrogen can be easily acetylated, benzoylated, or methylated, *N*-methylisatin, for example, being formed, thus showing the presence of the lactam structure. If, however, the red silver salt of isatin is treated with methyl iodide *o*-methylisatin is obtained. The lactim structure is also shown by warming a benzene solution of isatin with phosphorus pentachloride, when isatin chloride is obtained.



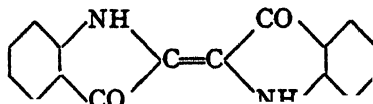
From a comparison of the absorption spectra of isatin and its N-methyl and O-methyl ethers, Hartley and Dobbie concluded that isatin possessed the lactam structure. Later work by R. A. Morton and E. Rogers and by R. G. Ault, E. L. Hirst and R. A. Morton¹ indicated that the spectra of the two methyl ethers show slight differences only and afford little information as to the structure of isatin. It has been found, however, that the C₂—O bond length is 1.21 Å, the length associated with the double bond in the carbonyl group. In isatin, therefore, the lactam form predominates.

Isatin gives a number of colour reactions. It condenses, for example, with thiophen to give the blue dye-stuff *indophenine*.

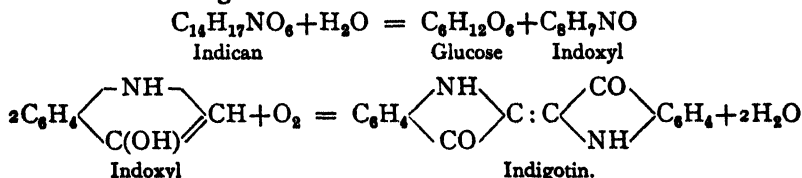
¹ *J.*, 1925, 2698; 1935, 1653.

Indigo Blue, Indigotin

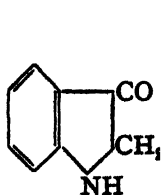
Indigo blue or indigotin is the chief constituent of commercial indigo, the earliest and one of the most important of dye-stuffs. It is mentioned by Dioscorides and Plinius, and in the thirteenth century Marco Polo described its preparation in India. The dye was rapidly adopted in Europe, and after the discovery of the sea route to India was imported in large quantities. Indigo is now obtained almost entirely by synthetic methods.



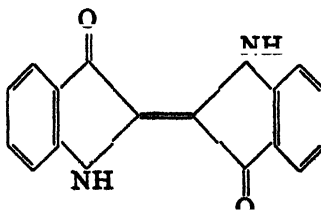
Indigo was formerly prepared from a variety of plants more particularly those of the genus *indigofera* (India, China, Central America). In these plants it is present in the form of **indican**, which has been shown by synthesis to be the glucoside of indoxyl¹ (3-β-glucosido-oxyindole). Under the influence of certain ferments or when treated with dilute acids it is hydrolysed into glucose and indoxyl, and the latter in contact with air is oxidised to indigotin.



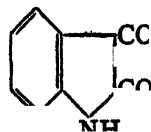
Structure of Indigotin.—The molecular structure for indigotin already given is deduced from a number of reactions and syntheses. It formed the climax of a series of researches on indole and its derivatives by Baeyer. Indigotin on dry distillation gives aniline and anthranilic acid, and is therefore a benzenoid derivative with carbon and nitrogen atoms attached directly to the nucleus in *ortho* positions. Since the sole oxidation product of indigotin is isatin (or derivatives of isatin) indigotin must contain an indole nucleus, or more correctly two indole nuclei, for analysis and vapour density measurements show the empirical



Indoxyl



Indigotin



Isatin.

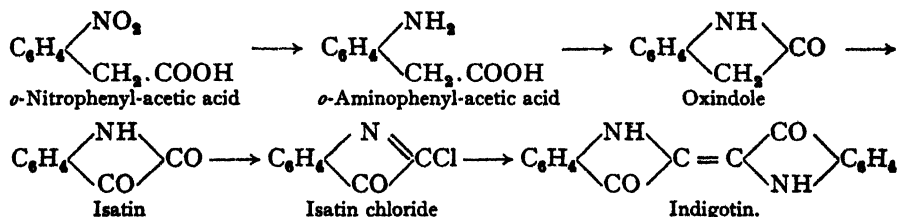
formula to be $\text{C}_{16}\text{H}_{10}\text{O}_2\text{N}_2$. This is confirmed by the conversion of indigotin into indole by distillation with zinc dust (Baeyer). The linkage of the two nuclei probably occurs at C₂ since indigotin is obtained by

¹ A. Robertson, *J.*, 1927, 1937.

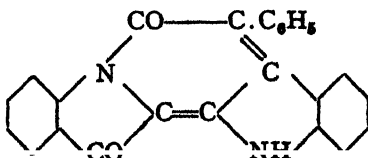
the oxidation of indoxyl. This is confirmed by an early synthesis of indigotin from *o*-dinitro-diphenyl-diacetylene. The starting-point in this case was *o*-nitrophenyl-propionic acid, which on boiling with water gave *o*-nitrophenyl-acetylene, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{C} \equiv \text{CH}$. The copper compound of the latter, on oxidation with potassium ferricyanide, was converted into *o*-dinitro-diphenyl-diacetylene, and this, on treatment with sulphuric acid added on two molecules of water, yielding a product from which on subsequent reduction indigotin was obtained.



Of the various syntheses that support the above formula, the first and historic synthesis of Baeyer may be mentioned. *o*-Nitrophenyl-acetic acid was reduced to *o*-aminophenyl-acetic acid, which was readily converted into its lactam, oxindole. The latter, on treatment with nitrous acid, gave isonitroso-oxindole, and the amino-oxindole obtained from this by reduction was transformed into isatin by the use of a mild oxidising agent. Treatment with phosphorus pentachloride gave isatin chloride, which with zinc dust was reduced to indigo blue.

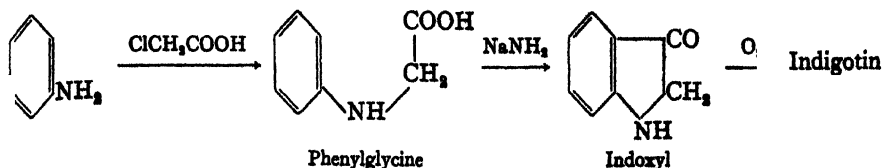


More recent research, though modifying, has confirmed the correctness of Baeyer's formulation. For example, the presence of the double bond between the two nuclei has been shown by ozonisation to isatin. Again indigotin should theoretically exist as two geometrical isomers, of *cis* and *trans* types respectively. The form generally obtained possesses a centre of symmetry¹ (see p. 37) and must therefore have the *trans* structure. This is in agreement with the fact that *trans* forms are more stable than the *cis* isomers, and with certain chemical properties of indigotin. Phenylacetyl chloride, $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{COCl}$ condenses with indigotin, a reaction that is most satisfactorily interpreted on the assumption of a *trans* structure.

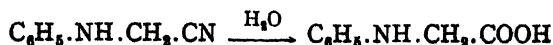
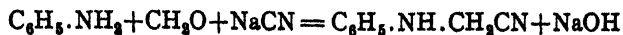


¹ Reis and Schneider, *Z. Krist.*, 1928, 68, 543.

sodamide is to destroy the water formed during the cyclisation and thus enables the process to go to completion. From the commercial point of




view this method is advantageous in that it utilises aniline instead of the more expensive anthranilic acid. The advantage was further emphasised when a cheaper process for the manufacture of phenylglycine was found.



Phenylglycine-nitrile is quantitatively prepared from aniline, formaldehyde, and sodium cyanide, and the nitrile then hydrolysed to phenylglycine. This is the basis of the present-day manufacture of indigotin.

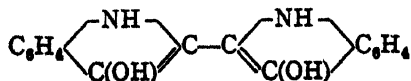
Properties of Indigotin

Indigo blue forms a dark blue powder possessing a reddish metallic lustre. In the light of our present knowledge of quinones and unsaturated diketones, it may be assumed that the colour of indigo is connected with

the presence of the complex  in the molecule, in which

the imido-groups play the part of auxochromes. The dye is insoluble in water, alcohol, ether, alkalis and dilute acids. It dissolves to a blue solution in hot aniline, and crystallises out from hot turpentine in blue plates. On sublimation it is obtained in coppery red prisms with a metallic glance. By bromination in nitrobenzene solution according to the proportion used, there is obtained **mono-**, or **dibromo-indigo** in which the bromine atoms enter into the positions para to the imino groups. Further bromination yields **5:5':7:7'-tetrabromoindigo**, *Ciba Blue 2 B*, in which the two positions ortho to NH are also substituted. The brominated dyes are marked by their intensity of colour and beauty of tint. The tetrabromo-compound is the most widely used halogenated indigo dye and gives faster blue shades than those of indigo. These and other substitution products can also be prepared from corresponding substituted raw materials by the methods already described for the synthesis of indigotin.

With reducing agents (see below) indigo blue takes up two atoms of hydrogen and is converted into **indigo white**, which is formulated as a *di-indoxyl*.



Method of Use as a Dye-stuff

Indigo is a **vat dye**; that is it is a water-insoluble dyestuff which by **vatting** is converted into a soluble form capable of being absorbed and retained by the fabric. Vatting is a reduction process and in this case 1 : 6-reduction—a rare occurrence—yields the dihydroxy-product Indigo White.



The new system contains only two conjugated double bonds and is therefore colourless. For this reason it is known as the leuco compound (leucos = white). It possesses phenolic character and dissolves in alkalis. Its importance lies in the fact that it is easily oxidised in alkaline solution back to the dyestuff, which can thus be implanted firmly on the fibre.

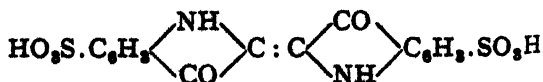
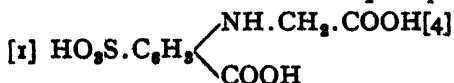
Indigo is employed as a vat dye in the following manner. Finely-divided indigo suspended in water is first reduced. According to the material to be dyed, this may be effected by use of fermentation methods or of various chemical reducing agents, such as ferrous sulphate, stannous chloride, grape sugar, zinc dust or hydrosulphite. The indigo white thus formed remains dissolved in the alkaline fluid.

The material to be dyed is then steeped in the solution and exposed to air, when oxidation takes place and the indigo white is converted into indigo blue, which is deposited on the threads.

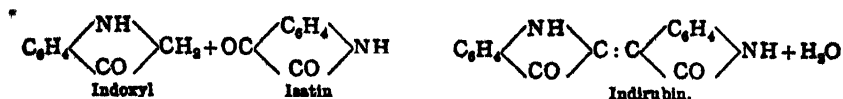
The earliest vats employed were fermentation vats, still in common use to-day for woollen goods, in which the dye-stuff is reduced by the action of micro-organisms in the presence of lime or alkalis. The best vat for cotton is the **hydrosulphite vat**, in which the reducing agent is the soluble sodium salt of hydrosulphurous acid, $\text{H}_2\text{S}_2\text{O}_4$.

In **cotton printing** with indigo, the dye suspended in concentrated caustic soda is pressed into contact with the fabric, which has previously been treated with a solution of glucose. The material is then exposed to the action of steam, when indigo white is formed. This penetrates into the threads, and on subsequent exposure to air is transformed into the blue dye.

In wool dyeing use is also made of the readily soluble sodium salt of indigo-disulphonic acid (see below), which is sent on to the market in the form of a paste under the name of **indigo carmine**. This substance contains one sulphonic group in each benzene nucleus, in the para-position to the NH group, as was shown by its synthesis by Heumann's method from anthranilido-acetic-*p*-sulphonic acid :



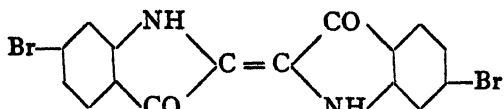
Indirubin, indigo red, occurs together with its structural isomeride indigo blue in natural indigo. It was synthesised by Baeyer by mixing weakly alkaline solutions of isatin and indoxyl, and may therefore be regarded as the indogenide of isatin :



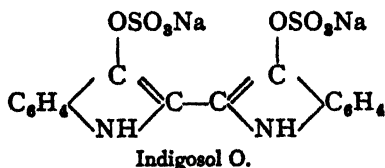
The compound is not stable towards reducing agents and is therefore of no use as a vat dye. This drawback is not present in tetrabromo-indirubin (*Ciba Heliotrope B*), obtained by direct treatment with bromine, nor in *Thioindigo Scarlet R* (see later) in which the imino-groups are replaced by sulphur atoms.

Baeyer described as **indogenides** those compounds in which an oxygen atom is replaced by the indogen group, $\text{C}_6\text{H}_5 \begin{array}{c} \diagup \text{NH} \\ \diagdown \text{CO} \end{array} \text{C} =$.

6 : 6'-Dibromo-indigo, of the formula



is a substance of particular interest, being identical with the *purple of the ancients* (Tyrian purple). This was proved by Friedlander by a direct comparison of the synthetic product with that prepared from the secretion of the Purple Snail, *Murex brandaris*, about one and a half grammes of the dye-stuff having been isolated from 12,000 snails. It is the only bromo-organic compound found in a living organism. It forms crystals of a coppery glance, and by interaction with caustic soda and sodium hydrosulphite yields a vat of weak yellow tint from which cotton is dyed a reddish-violet shade. This striking displacement of the colour of indigo results not only from the introduction of bromine, but also of chlorine and methoxyl groups in the 6 : 6'-positions. Hence substitution in the *p*-position to the CO-group exerts a quite specific influence. In the same way the effect of *p*-substitution may be traced in the derivatives of thio-indigo.

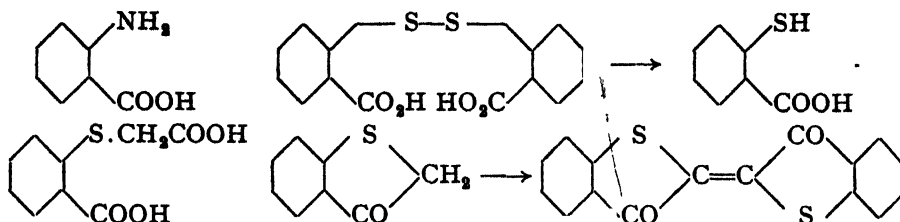


Indigosols.—In order to obviate the shrinking of woollen and silk goods when used with indigo in alkaline vats, and to relieve the dyer of the vatting process, the stable leuco form **solubilised indigo** was introduced by Bader in 1924. Indigo is reduced to indigo white and the latter treated with pyridine-sulphur trioxide, when a sulphuric ester of leuco-indigotin is formed. The sodium salt of this compound is **Indigosol O**. It is stable in neutral solutions, from which it is directly absorbed by wool, silk or

cotton. The absorbed compound is then treated on the fabric with an acid oxidising agent, when the sulphuric ester groups are hydrolysed and the regenerated indigo white converted into indigotin. Other indigosols may be prepared from derivatives of indigo in a similar manner.

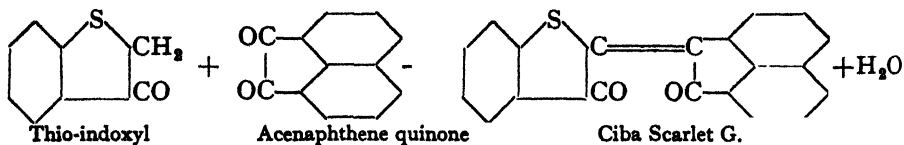
Thioindigo Dyes

Dye-stuffs of this group were discovered by Friedländer in 1906, as a result of experiments directed towards replacing the imino groups of indigo by sulphur atoms. The simplest compound, **thioindigo** (*thioindigo red B*, *Ciba Red*) is prepared from anthranilic acid in the following stages. By diazotisation and treatment with sodium disulphide it is converted into dithio-salicylic acid, which on reduction with iron and alkali yields thio-salicylic acid. The latter combines with chloracetic acid to form

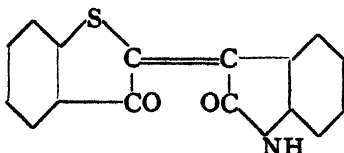


phenyl-thioglycollic-*o*-carboxylic acid, and this on fusion with alkali or sodamide gives thio-indoxyl. On oxidation with air or potassium ferricyanide, thio-indoxyl is converted into thio-indigo, a bright bluish red dye which resembles indigo in its fastness to light and oxidation. Thio-indigo can be separated chromatographically into the *cis*-(orange-yellow) and *trans*-(red-purple) forms.¹

Other dyes of this group are made by condensing thio-indoxyl with various ketonic compounds. Thus *Ciba Scarlet G*, an excellent if somewhat expensive red dye, is obtained by use of acenaphthene quinone. It is of special value for printing.

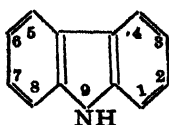


Thio-indigo Scarlet R is made in a similar manner from thio-indoxyl and isatin.



In this compound the bluish shade of thio-indigo has disappeared, to be replaced by a brilliant scarlet.

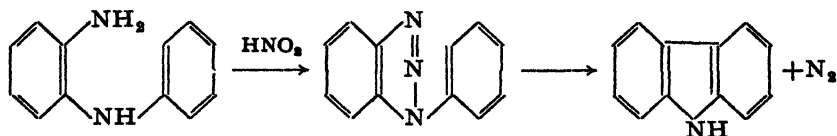
¹ G. M. Wyman and W. R. Brode, *J.A.C.S.*, 1951, 73, 1487.

Carbazole ¹

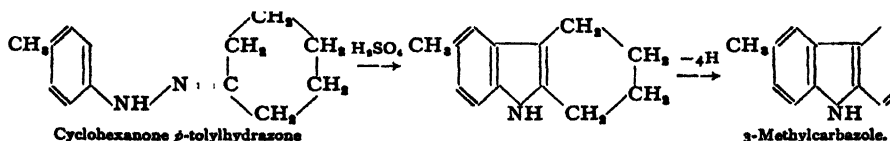
As has been mentioned on p. 591, carbazole is found in crude anthracene. The hydrogen atom of the imino-group resembles that of pyrrole in being replaceable by metals, and hence carbazole may be isolated from the above source in the form of potassium carbazole, $C_{12}H_8NK$, by distilling crude anthracene over potassium hydroxide. Another method involves treatment with suitable solvents.

Substituted carbazoles are best prepared by one or other of the following methods.

1. *Graebe-Ullmann Method*.—*o*-Aminodiphenylamines are treated with nitrous acid and the resulting phenylazimido-compounds heated to give nitrogen and a carbazole.



2. *Borsche's method*.—This is an extension of Fischer's indole synthesis and has been widely used in the preparation of substituted carbazoles (Plant and Tucker). Cyclohexanone phenylhydrazones, when heated with dilute sulphuric acid give tetrahydrocarbazoles, which on dehydrogenation with chloranil, quinoline and sulphur, or palladised charcoal give the corresponding carbazoles.



Carbazole crystallises in leaflets or plates which melt at 245° . Like pyrrole it is a very weak base and gives a deep red colour with a pine splint moistened with hydrochloric acid. With isatin and sulphuric acid a blue coloration is produced.

Carbazole is an extremely stable compound. It may be distilled unchanged over zinc dust at a red heat, and is not attacked by concentrated hydrochloric acid or alcoholic potash, even at 300° . Towards potassium permanganate it behaves as a fully saturated substance.

¹ See Barclay and Campbell, *Chem. Reviews*, 1946, 40, 359.

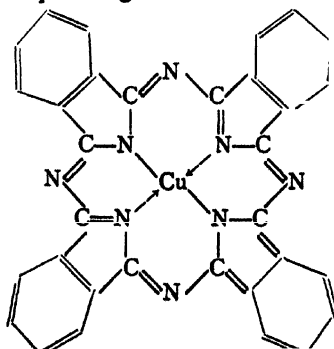
Phthalocyanines

A remarkable series of complex metallo-organic pigments known as **phthalocyanines** has recently been discovered, which contain the uni

structure, $C_6H_4 \begin{array}{c} \diagup C-N \\ \diagdown C-N \end{array}$ and are thus derivatives of iso-indole. They

give blue or green colours characterised by great brilliance and fastness to acids and alkalis and are of wide application. The first phthalocyanine, an iron compound, was isolated by chance¹ in 1928 as a dark blue crystalline substance during the preparation of phthalimide by passing ammonia into molten phthalic anhydride contained in an iron vessel. The iron was firmly attached to the molecule and was not even displaced by treatment with cold concentrated sulphuric acid. Later investigation by Linstead and his co-workers² led to the preparation of other derivatives and to the elucidation of their structure.

One of the best known of these compounds is **Monastral Fast Blue B.S.**, *copper phthalocyanine*, a bright blue pigment which is employed chiefly for colouring leather, printing ink and paints. The molecular structure given below is supported by the results of X-ray analysis. It is seen to be built up of four iso-indole units linked so as to form a 16-membered arrangement of alternating carbon and nitrogen atoms. The copper atom lies in the centre and is attached to four adjacent nitrogen atoms by two co-valent and two co-ordinate valency bonds, the latter being indicated by arrows (see pp. 20, 21). The molecule is extremely stable. Copper phthalocyanine is unchanged by cold concentrated sulphuric acid and may be sublimed at 580°. With hot concentrated nitric acid it decomposes to yield phthalimide, the same product being obtained with cold acid permanganate solution.



Monastral Fast Blue

Monastral Blue may be prepared (a) by heating phthalonitrile with copper or copper salts, or (b) by passing ammonia into molten phthalic anhydride or phthalimide in the presence of copper compounds. By

¹ By Scottish Dyes, Ltd.

² See also J. M. Robertson, *J.*, 1935, 615.

similar methods other metallic compounds are prepared, their colours depending on the metals used. For instance, lead phthalocyanine is a green pigment.

Phthalocyanine, represented by the above formula with copper removed and the two nitrogen co-valencies satisfied by two hydrogen atoms, may be prepared by dissolving the less stable magnesium phthalocyanine in cold concentrated sulphuric acid and pouring the solution on to ice. It has a greenish-blue colour with a beautiful purple reflex, and resembles the metallic derivatives in being very stable and insoluble. Reference to the formulæ given for the porphyrins on p. 815 reveals a close similarity to those of the phthalocyanines.

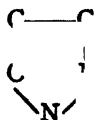
III Azoles

The azoles are five-membered cyclic systems which contain in addition to carbon and nitrogen at least one other hetero-atom, sometimes indicated by the name. Thus oxazole contains an oxygen atom; thiazole a sulphur atom; and pyrazole a nitrogen atom. Hence they may be derived from the compounds pyrrole, furan and thiophen, described in the previous chapter, by replacing methine groups with nitrogen atoms. Only the most important of these will be described in detail.

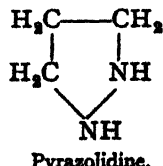
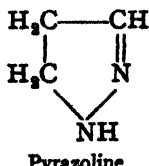
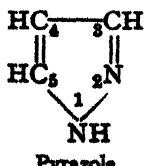
I.—PYRAZOLE GROUP

This group comprises all those compounds, the molecules of which contain a ring composed of three carbon and two nitrogen atoms arranged as follows.

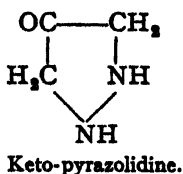
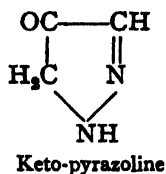
The parent substance of these compounds, pyrazole, is a pyrrole in which a methine group has been replaced by nitrogen.



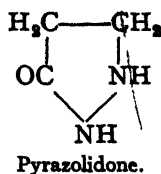
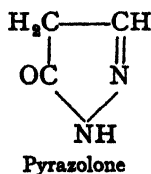
For this reason the *nomenclature of the pyrazole group* is based on that suggested by Knorr for pyrrole derivatives. Just as dihydro-pyrrol is known as pyrroline and tetrahydro-pyrrole as pyrrolidine, so the dihydro pyrazoles are termed *pyrazolines* and the completely reduced tetrahydro derivatives, *pyrazolidines*.



The position of a substituent group in the pyrazole nucleus is indicated by the numbers 1 to 5. Numbering commences with the nitrogen atom of the imino-group and proceeds in an anti-clockwise direction to the second nitrogen atom, as in the above formula. Ketonic derivatives of pyrazoline and pyrazolidine are usually divided into two classes, viz., 4-derivatives or true ketones, such as keto-pyrazoline and keto-pyrazolidine,



and the 3- and 5-derivatives, which are cyclic acid amides. For the latter Knorr proposed the names pyrazolone and pyrazolidone.

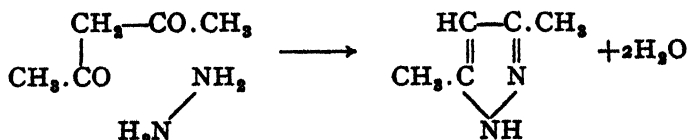


Our knowledge of the pyrazole series is largely due to the work of Knorr, who described the first representatives of this group in 1883. The physical properties of these compounds and the applications which many of them, such as antipyrine, find in medicine, lend a special interest to this chapter of organic chemistry. For this reason the pyrazole group, after its discovery by Knorr, was investigated in a number of directions and—thanks to the ease with which the pyrazole ring can be formed—these efforts met with considerable success. Among other results, it may be mentioned that Knorr established the existence of a peculiar type of isomerism in this series.

General Methods of Preparing Pyrazole Derivatives

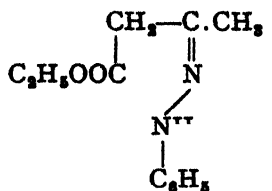
Most pyrazole syntheses involve the use of hydrazine or its derivatives (Knorr) or aliphatic diazo-compounds (Buchner).

1. Hydrazines are condensed with β -dicarbonyl compounds (β -diketones and β -keto-aldehydes).

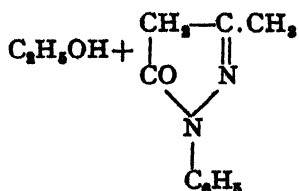


This has proved the most fruitful of all reactions devised for the preparation of pyrazole derivatives. On the one hand, as basic component, we may employ hydrazine hydrate itself or any primary hydrazine, and

on the other, the numerous β -diketones and β -keto-aldehydes which can readily be prepared synthetically: esters of β -ketoic acids may also be used, as in the preparation of 1-phenyl-3-methyl-5-pyrazolone.

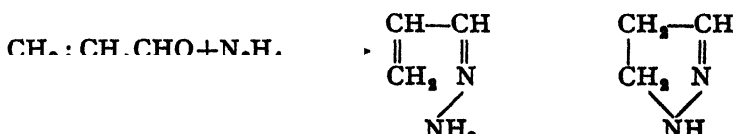


Phenylhydrazone of
acetylacetone



1-Phenyl-3-methyl-5-pyrazolone

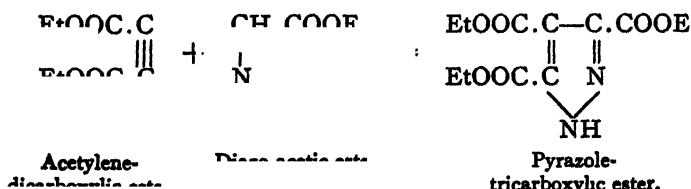
2. Hydrazines condense with $\alpha : \beta$ -unsaturated aldehydes, ketones, or acids to give derivatives of pyrazole or pyrazoline. Thus the parent compound of the latter class, pyrazoline, is formed from acrolein and hydrazine hydrate. The acryl-hydrazine first formed isomerises spontaneously into the cyclic base:



The principle of the above syntheses may be summarised in the following statement:—

Compounds containing two CO-groups, or a CO- and a COOH-group, in the β -position to one another, or two doubly-linked carbon atoms adjacent to a COOH- or CO-group, react with hydrazines to give pyrazole derivatives.

3. Diazo-acetic ester and other aliphatic diazo-compounds such as diazomethane react with ethylenic and acetylenic compounds to form pyrazole derivatives



Acetylene-
dicarboxylic ester

Diazo-acetic ester

Pyrazole-
tricarboxylic ester.

Acetylene and diazomethane react in a similar manner (von Pechmann). This constitutes the simplest synthesis of pyrazole.



These simple syntheses prove that the atoms in the pyrazole ring are in agreement with the formulæ assumed above.

The simpler pyrazole compounds are frequently obtained from their derivatives. For example, the carboxy groups may be removed from pyrazole carboxylic acids by heating the latter above their melting-points. Pyrazole may conveniently be prepared by this method from pyrazole-3 : 5-dicarboxylic acid which is readily obtained by synthesis.

Properties of Pyrazole and its Derivatives

The similarity in the formulæ of pyrazole and pyrrole does not extend to their properties. Pyrazole differs strongly from pyrrole in its remarkable stability and more definitely basic character.

Pyrrole turns brown in air, resinifies with extraordinary ease, and on reduction is converted into di- and tetrahydro-derivatives. Pyrazole, which crystallises in long colourless needles, m.p. 70° and b.p. 185° , is much more resistant to change.

In pyrrole the basic character is barely evident (pK_a 0.4). On the other hand, pyrazole, although it gives no reaction with litmus and can be removed from weakly acid solutions by a current of steam, nevertheless yields well-defined salts with acids.

All the chemical properties of pyrazole show it to be more nearly allied to pyridine and benzene than to pyrrole. It exhibits, to an even greater degree than thiophen, those peculiarities which were first observed in the aromatic series and are therefore associated with the term "aromatic character."

A number of facts established by Knorr clearly illustrate the aromatic character of pyrazole :

1. Fuming sulphuric acid converts pyrazole into a sulphonic acid, which in its reactions shows certain resemblances to the aromatic sulphonic acids.

2. In halogen derivatives of pyrazole a halogen atom attached to the nucleus is even more firmly held than in benzene derivatives.

3. When pyrazole is treated with concentrated nitric acid, hydrogen is readily exchanged for a nitro-group. Like the aromatic nitro-compounds, 4-nitro-pyrazole and its derivatives can be reduced to amino-compounds.

4. Amino-pyrazole resembles the aromatic bases in its behaviour. It gives a colour reaction with a solution of bleaching powder, and is readily diazotised.

5. Diazo-pyrazoles can be coupled with phenols to form azo-dyes in exactly the same manner as the aromatic diazo-compounds. They differ from most of the latter in the stability of their salts in aqueous solution. On boiling these solutions there is no visible evolution of nitrogen; this only occurs on prolonged heating at a higher

temperature. Diazo-pyrazoles, however, do not undergo the usual "diazo-reactions."

6. Pyrazolone, or 5-hydroxy-pyrazole, has a pronounced phenolic character.

7. Towards oxidising and reducing agents pyrazole shows the same remarkable stability as benzene.

8. Homologues of pyrazole resemble those of benzene in being readily oxidised to the corresponding carboxylic acids.

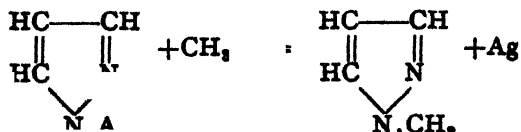
Hence it will be seen that the analogy between pyrazole and benzene is a far-reaching one.

In smell and other properties the alkyl derivatives of pyrazole so closely resemble pyridine bases that on casual examination they may easily be mistaken for them. The carboxylic acids of pyrazole also possess many points in common with those of pyridine. For example, when polycarboxylic acids of pyridine are heated, they part with carbon dioxide to give the mono-acid, and it is found that the carboxyl group in the α -position to nitrogen is the first to be removed. By a repetition of this process the monocarboxylic acid is converted into pyridine. The properties of 3- (or 5-) pyrazole-carboxylic acid are very closely allied to those of pyridine α -carboxylic acid (see Picolinic Acid).

Owing to the basic character of pyrazole, its resemblance to pyridine is more evident than its resemblance to benzene. Pyrazole is a weak secondary base; as such it may be acetylated, benzoylated, and converted into derivatives of urea and urethane.

It unites with alkyl iodides to form crystalline ammonium compounds. These are of importance in the preparation of homologues of pyrazole, as under the influence of heat the alkyl radical is transferred from nitrogen to a carbon atom of the nucleus. The Hofmann synthesis of aniline homologues (p. 468) can therefore be applied to the pyrazole series. As will be seen later, this reaction is also of value in the pyridine group.

The silver compounds are readily formed by all pyrazoles containing a free imino-hydrogen atom, and are useful for the preparation of N-alkyl substituted derivatives by double decomposition with alkyl iodides. Thus silver pyrazole and methyl iodide yield 1-methyl-pyrazole.

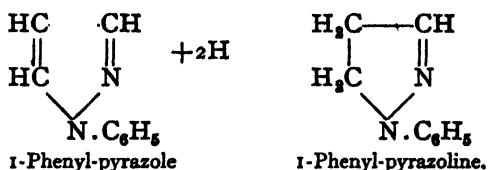


It has already been mentioned that the pyrazole nucleus is stable towards oxidising agents. The alkyl groups attached to the ring in homologues of pyrazole may be successively oxidised to carboxyl groups by use of potassium permanganate.

In 1-phenyl-pyrazoles the benzene nucleus is more readily oxidised away than the pyrazole nucleus, as is shown by the formation of pyrazole when 1-phenyl-pyrazole is oxidised with permanganate in sulphuric acid solution (Knorr). As in the aromatic series, the benzene ring is still more easily disrupted if its stability is first lowered by the introduction of an amino or hydroxyl group. For example, the benzene ring of 1-amino-phenyl-3-methyl-pyrazole is much more readily attacked than that of 1-phenyl-3-methyl-pyrazole. A remarkable point is the stability of pyrazole derivatives under these conditions as compared with corresponding derivatives of pyrrole, the latter being completely oxidised by potassium permanganate.

The action of nascent hydrogen (from sodium and alcohol) varies with different compounds of the pyrazole group. Pyrazole itself and its homologues are apparently not attacked by sodium and alcohol.

1-Phenyl-pyrazole and its homologues, *i.e.*, those derivatives formed by the interaction of phenylhydrazine and β -diketo-compounds, have been shown by Knorr to be reduced to pyrazoline derivatives.



Pyrazoline bases obtained from phenylhydrazine are changed by oxidising agents, such as chromic acid, nitrous acid, ferric chloride, and hydrogen peroxide, into characteristic dyes varying from red to blue in colour. This reaction, described by Knorr as the **pyrazoline reaction**, may be used for the detection of pyrazole and pyrazoline bases derived from phenylhydrazine.

Pyrazoline and its Derivatives.—Pyrazoline derivatives differ considerably in their properties from those of pyrazole, owing to their much lower stability. This is another indication of the aromatic nature of pyrazole, since it is almost a characteristic of aromatic compounds that the addition of two hydrogen atoms to the ring results in diminished stability.

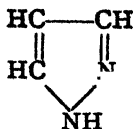
The pyrazolines give the reactions of aliphatic derivatives, resembling unsaturated compounds in their behaviour towards permanganate and nascent hydrogen.

Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. The parent substance, **pyrazoline**, an oil of boiling-point 144° , is the most stable of all these compounds.

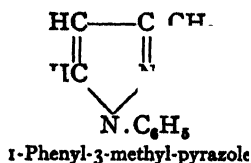
The *pyrazolidines*, or completely reduced pyrazoles, have not been thoroughly investigated owing to their instability. They possess strong reducing properties and readily give up hydrogen to form pyrazolines.

Derivatives of Pyrazole—Tautomerism in the Pyrazole Series

As the result of an investigation into the synthetic derivatives of 1-phenyl-pyrazole, Knorr assigned to the then unknown pyrazole the following constitution:—



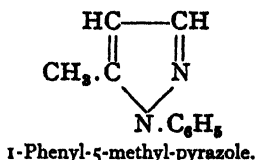
The problem of the structure of pyrazole entered a new phase in 1893, when Knorr and Macdonald showed that the oxidation of the well-known isomeric compounds 1-phenyl-3-methyl-pyrazole and 1-phenyl-5-methyl-pyrazole gave one and the same methyl-pyrazole of boiling-point 205°.



Crystalline, m.p. 37°.

B.p. 254° to 255°.

Methiodide, m.p. 141°.

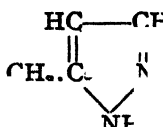
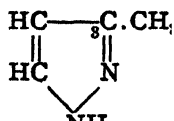


Colourless oil, b.p. 254° to 255°.

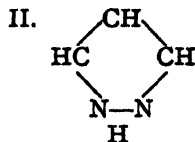
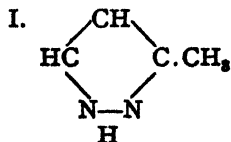
Does not solidify at -20°.

Methiodide, m.p. 296°.

By this method it is therefore not possible to obtain the two methyl-pyrazoles of the formulae



corresponding to the above phenyl-methyl-pyrazoles. In other words, in the pyrazole molecule positions 3 and 5 are completely equivalent, and the methyl-pyrazole just mentioned was described by Knorr as 3-(5)-methyl-pyrazole and formulated as I below.



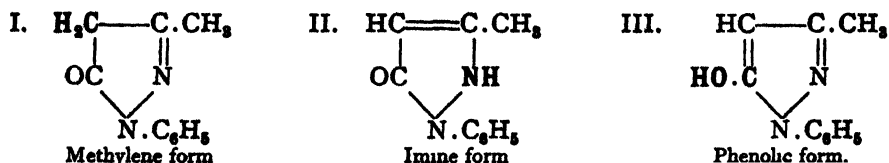
There is still considerable controversy over the mechanism of pyrazole tautomerism.¹

It should be noted that in consequence of the symmetry of the pyrazole molecule (II) only two C-methyl-pyrazoles are possible. The symmetry, however, is destroyed in 1-phenyl-pyrazole, which gives rise to three C-methyl derivatives.

¹ See for example, H. T. Hayes and L. Hunter, *J.*, 1941, 1.

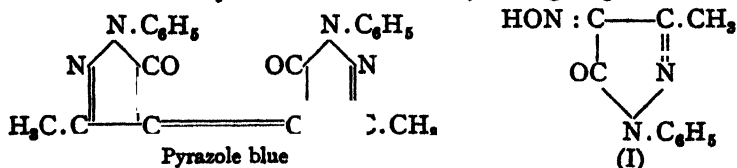
In addition to the above tautomerism of 3-(5)-methyl-pyrazole, a second type of tautomerism has been observed in the pyrazole series in 1-phenyl-3-methyl-5-pyrazolone, the parent compound of antipyrine, which is usually formulated as I. It is prepared in large quantities as an intermediate product in the manufacture of antipyrine, by condensing acetoacetic ester with phenylhydrazine (see p. 689).

This extremely reactive compound may react in the three tautomeric forms shown below, thus giving rise to what Knorr termed double tautomerism.



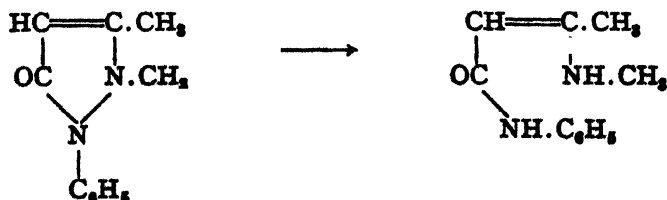
1-Phenyl-3-methyl-5-pyrazolone itself is known only in one form. Whether prepared by synthesis or from a derivative corresponding to one or other of the above three types, it is always obtained in the form of a substance of melting-point 127° , crystallising in white prisms. Which of the above three formulæ represents this compound has not yet been established with certainty, but numerous derivatives are known corresponding to each type.

Many derivatives of phenyl-methyl-pyrazolone possess the *methylene structure*. An example is *pyrazole blue*, which is readily obtained by the gentle oxidation of the pyrazolone and represents the indigo of the pyrazole series. The presence of a methylene group activated by a



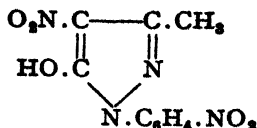
neighbouring carbonyl group is shown by the formation of the isonitroso-derivative (I) by treatment with nitrous acid.

The *imine structure* is only found in the group of phenyl-methyl-pyrazolone derivatives known as antipyrines (see next page). Proof of the imine structure of the antipyrines is found in the disruption of antipyrine by means of sodium to give the anilide of β -methylamino-crotonic acid.



In forming O-benzoyl derivatives the pyrazolone reacts in the *phenolic form*.

In conclusion, it may be mentioned that certain nitro-derivatives of phenyl-methyl-pyrazolone, such as *4-nitro-1-p-nitrophenyl-3-methyl-pyrazolone*, known as *picrolonic acid*,

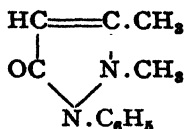


were also regarded by Knorr as nitrophenols, owing to their similarity to picric acid. Picrolonic acid yields very sparingly soluble salts, which in their properties show a close resemblance to the picrates. They are usually even less soluble than the latter, and may be employed with advantage for the isolation and identification of bases.

The arguments which lend support to each of the three competing formulæ of phenyl-methyl-pyrazolone lead to the conclusion that the acidic hydrogen atom and the double bonds occupy no fixed positions in this compound. It is the peculiar mobility of this hydrogen atom which enables tautomeric changes to be completed with such ease.

Analogous rearrangements of bonds, but without any movement of hydrogen, are also shown by antipyrine in certain addition reactions.

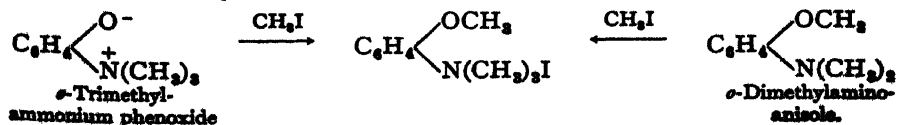
Antipyrine, 1-phenyl-2 : 3-dimethyl-5-pyrazolone,



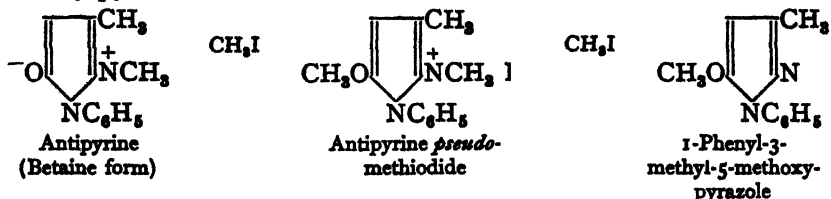
is the most important member of the pyrazole group, and is used extensively in medicine as a febrifuge. It is prepared industrially by heating 1-phenyl-3-methyl-5-pyrazolone with methyl iodide and methyl alcohol at 100° under pressure; the hydriodide of antipyrine is thus produced, from which sodium hydroxide liberates antipyrine itself. A method of preparing antipyrine which throws light upon its constitution consists in the condensation of acetoacetic ester with symmetrical phenyl-methyl-hydrazine.

It crystallises in white plates, m.p. 113°, and dissolves readily in water and alcohol. The aqueous solution is coloured red by ferric chloride, and green by nitrous acid. Antipyrine is a strong monacid base and readily forms salts, most of which are easily soluble in water.

Antipyrine shows some similarity to the *phenol betaines*, a typical example of which is *o*-trimethylammonium phenoxide. This substance reacts with methyl iodide in the presence of sodium hydroxide to give a quaternary iodide identical with that obtained by the action of methyl iodide on *o*-dimethylamino-anisole.

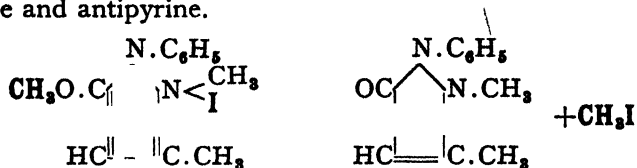


At ordinary temperatures alkyl iodides unite with antipyrine in the same manner, *i.e.* the alkyl group attaches itself to the oxygen atom. Antipyrine and methyl iodide, for example, react to form the pseudo-methiodide, which is identical with the methiodide of 1-phenyl-3-methyl-5-methoxy-pyrazole :



This reaction was formerly cited as evidence in support of a betaine formula for antipyrine, but this is not in harmony with the properties of antipyrine. It does indicate, however, that antipyrine is a resonance hybrid with the betaine structure as one of the contributing forms.

On being fused, the pseudo-alkiodides of antipyrine do not break up, as might be expected, into alkyl iodide and a phenolic ether, but into alkyl iodide and antipyrine.



Antipyrine is also regenerated from the pseudo-methiodide by the action of alkalis, slowly in the cold and more rapidly on heating.

Certain other derivatives of this type are of importance, *e.g.* **salipyrine** or antipyrine salicylate, **tolypyrine** or *p*-tolyl-dimethyl-pyrazolone, and **pyramidone** or 4-dimethylamino-antipyrine. These and other derivatives are employed medicinally, particularly as substitutes for antipyrine.

Indazoles or Benzo-pyrazoles

The ring system of the indazoles consists of a condensed benzene-pyrazole nucleus, and these compounds thus stand in the same relationship to the pyrazoles as the indoles to the pyrroles. Although the imino-hydrogen atom in indazole is not definitely located on either nitrogen atom, the parent compound gives rise to two series of N-derivatives, *e.g.* the 1- and 2-N-methylindazoles. The position of substituents is indicated by numbers, as in the following formula.

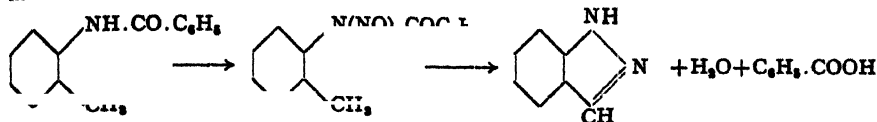


The structure of indazole has been intensively studied by Auwers and co-workers¹ and is still a matter of controversy. Structure A is preferable to structure B.²

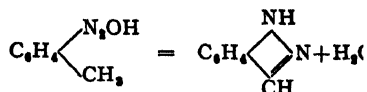
¹ *Ann.*, 1937, 527, 291.

² Barclay, Campbell and Dodds, *J.*, 1941, 113.

Indazole, discovered by Fischer and Tafel, is a crystalline compound, m.p. 146°, b.p. 270°. It may be prepared from benz-*o*-toluidide by dissolving it in acetic acid and acetic anhydride and passing in nitrous fumes; the resulting nitroso-compound, when heated in dry benzene, loses water and benzoic acid to form indazole, which is extracted with hydrochloric acid and then precipitated by addition of alkali. Indazole is soluble in hot water.



It is also obtained by removing the elements of water from *o*-toluene-diazo-hydroxide

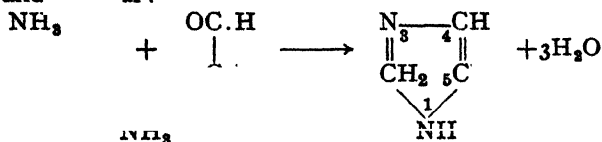


A large number of indazoles substituted in the benzene nucleus have been prepared by this method, by starting from substituted *o*-toluene-diazo-hydroxides. The diazo-compounds prepared from nitrated and brominated *o*-toluidines have a strong tendency to form rings of this type.

II.—IMINAZOLE OR GLYOXALINE GROUP

The ring system of the iminazoles, like that of the pyrazoles, consists of three carbon and two nitrogen atoms. In this case, however, the latter are not adjacent but are separated by a carbon atom. Hence iminazoles may be regarded as cyclic amidines, derived from the complex $\text{HN}=\text{CH}-\text{NH}_2$.

Glyoxaline, the parent compound of the series, is formed by the action of ammonia on glyoxal, and is also known as **iminazole**. In this reaction it is assumed that a part of the glyoxal is first broken up to give formic acid and formaldehyde, and that the latter then condenses with the ammonia and formalal:



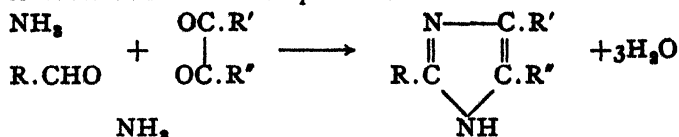
The figures attached to the formula indicate the numbering generally used.

Glyoxaline is more conveniently prepared by allowing formaldehyde and excess of ammonia to interact with dinitro-tartaric acid, when a good yield of ammonium glyoxaline-dicarboxylate is obtained, from which by addition of hydrochloric acid free *glyoxaline-dicarboxylic acid* is precipitated. The acid when heated to 300° decomposes smoothly into carbon dioxide and glyoxaline.

Glyoxaline forms prisms, m.p. 88° to 89° and b.p. 255° It is a weak base, and when warm possesses a faint fishy smell.

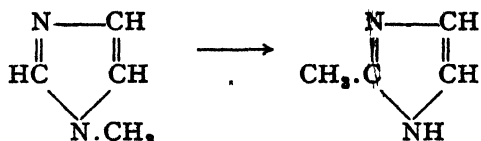
Substituted glyoxalines are prepared by a method analogous to that

employed for glyoxaline, by the action of ammonia and aldehydes on glyoxal or other 1 : 2-diketo compounds.



Properties of the Glyoxalines.—Glyoxalines are stronger bases than the isomeric pyrazoles, as may be seen from their basic pK_a values (glyoxaline 7.03, pyrazole 2.53).

The imino-hydrogen atom of glyoxaline can be replaced by metals and alkyl radicals, the latter by the action of alkyl halides. When passed through red-hot tubes these N-alkylglyoxalines isomerise to 2-alkyl-glyoxalines.



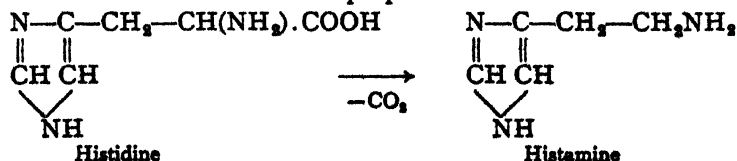
Glyoxaline exhibits tautomerism similar to that of pyrazole. Positions 4 and 5 are equivalent and as a result only one methyl compound corresponding to 4- or 5-methyl-glyoxaline is known.

Occurrence of Glyoxalines in Nature.—It was shown by Pinner that the alkaloid *pilocarpine*, present in jaborandi leaves (of *Pilocarpus pennatifolius*), is a derivative of N-methyl-glyoxaline. Other naturally occurring iminazole derivatives, such as caffeine, theobromine and theophylline, have already been described under the purine group. The purines, in fact, contain a nucleus formed by the fusion of an iminazole ring with a pyrimidine ring. The discovery of a remarkable transformation from the sugars to the iminazole group (see p. 318) lends additional interest to this series from the physiological as well as the chemical standpoint. Other glyoxaline derivatives of biological importance are histidine and histamine and the dipeptides carnosine and anserine (p. 251).

Histidine, α -amino- β -iminazyl-propionic acid, is a common decomposition product of proteins. It has been synthesised.

β -Iminazyl-ethylamine, *histamine*, is of biochemical interest. It is formed from histidine by bacterial putrefaction, and can therefore be isolated from the putrefaction products of proteins.

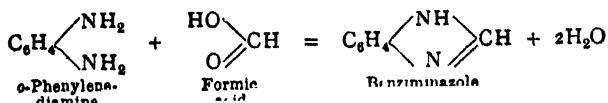
Histamine may be responsible for certain allergic reactions such as asthma, and a number of compounds, *anti-histamines*, which prevent or inhibit these reactions have been prepared.



It is found in the fresh mucous membrane of the small intestine; and is also present in preparations of ergot, where it is of importance in connection with the activity of the drug, as it causes contraction of the muscles of the uterus. The base has been prepared synthetically.

Benziminazoles¹

These compounds contain a condensed glyoxaline-benzene structure, and bear to the glyoxalines the same relationship as the indoles to the pyrroles. They are cyclic *o*-amidines of the benzene series, and are formed by the condensation of *o*-phenylene diamine and its substitution products with carboxylic acids or their anhydrides, *e.g.*,

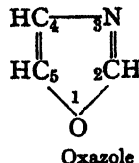
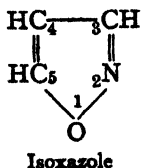


Benziminazole, m.p. 170°, is obtained by the above method and crystallises in colourless needles.

The basic character of the benziminazoles is not quite so marked as that of the glyoxalines. They are also weakly acidic and generally soluble in aqueous alkalis with the formation of N-metallic compounds. Like the glyoxalines they are attacked by benzoyl chloride and caustic soda, yielding dibenzoylated *o*-diamines. Towards oxidising and reducing agents they are very stable. An important derivative is vitamin B₁₂, which on hydrolysis yields 5 : 6-dimethylbenziminazole.

III. ISOXAZOLES, OXAZOLES, AND THIAZOLES

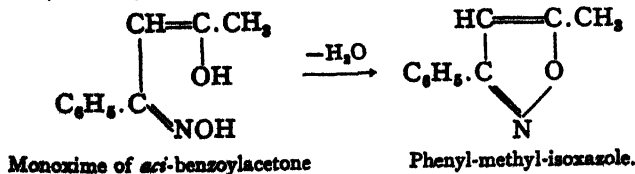
Cyclic compounds with three carbon atoms linked with one nitrogen and one oxygen atom are termed **isoxazoles** when the nitrogen and oxygen are adjacent, and **oxazoles** when these atoms are separated by one of carbon. Replacement of the oxygen atom by one of sulphur in



oxazoles gives the **thiazoles**. Neither the parent compounds nor their derivatives have been found in nature.

Isoxazoles

The isoxazoles are frequently obtained by loss of water from isonitroso compounds (oximes); *e.g.* from the oximes of β -diketones.

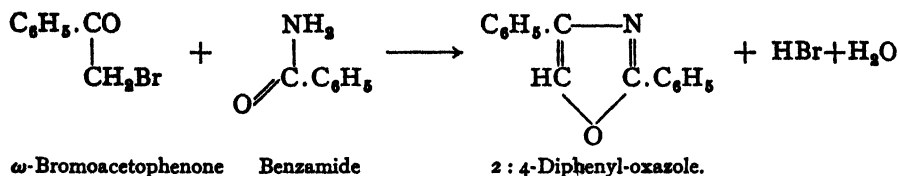


¹ J. B. Wright, *Chem. Reviews*, 1951, 48, 397.

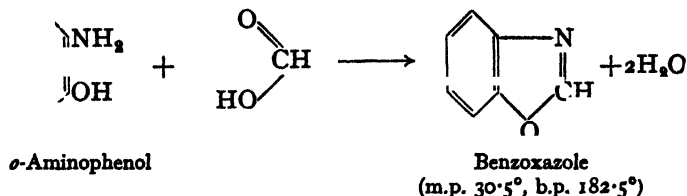
The parent compound is prepared by the reaction of hydroxylamine hydrochloride with propargyl aldehyde, $\text{CH}:\text{C}.\text{CHO}$. Isoxazoles are weak bases. Substituted isoxazoles played an important part in elucidating the mechanism of the Beckmann transformation (p. 53).

Oxazoles

A general method for the preparation of oxazoles is by the interaction of acid amides and α -halogeno-ketones.



The **benzoxazoles** may be compared to the benziminazoles, and are obtained from *o*-aminophenols by condensation with carboxylic acids (*cf.* formation of benziminazoles).

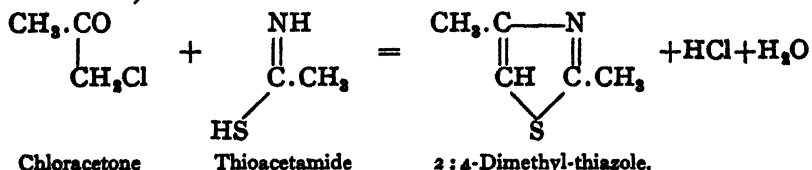


Benzoxazoles are weak bases, and undergo ring-fission when heated with hydrochloric acid, yielding aminophenols and carboxylic acids.

Thiazoles

Thiazoles and their derivatives are found in nature. Cleavage of vitamin B_1 by sulphite gives 4-methyl-5-(β -hydroxyethyl)-thiazole (p. 843) while penicillin is a thiazolidine derivative. Other thiazoles are valuable medicinals, sulphathiazole being one of the important sulpha drugs.

Thiazoles are formed by the interaction of thioamides and α -chloro-ketones or α -chloro-aldehydes (Hantzsch). (Compare method given above for oxazoles.)

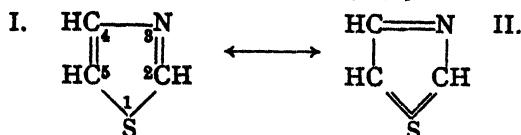


If thiourea is used in this reaction 2-amino-thiazoles are formed, which on treatment with nitrous acid and alcohol exchange the amino-group for hydrogen, with the production of thiazoles.

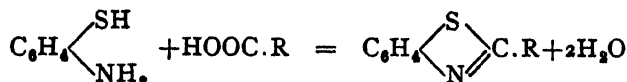
2-Aminothiazole, an intermediate in the preparation of sulphathiazole, is prepared similarly from thiourea and chloroacetaldehyde (generated

in situ from α : β -dichloroethylether). It undergoes diazotisation and from the resulting diazonium salts 2-chloro- or 2-bromo-thiazole or thiazole itself may be obtained. Thiazole is a mobile, volatile liquid, b.p. 117°, with a smell like pyridine. It is less basic than the latter.

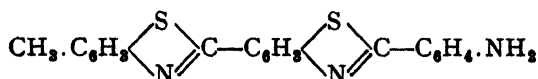
Thiazole stands in the same relationship to pyridine as thiophen does to benzene. As has already been shown on p. 669, the last two compounds possess many properties in common and a similar resemblance exists between thiazole and pyridine. Thiazole is usually represented as in I, although recent work by Erlenmeyer¹ indicates that it is more correctly regarded as a resonance hybrid of I and II. This formulation is in better agreement with the behaviour of the sulphur atom, which is not that of divalent sulphur, and with the fact that the double bonds do not appear to be fixed in the 2:3- and 4:5-positions.



Benzo-thiazoles resemble the quinoline bases, and correspond in their composition to the benzoxazoles and benziminazoles. They are produced by the action of acids on *o*-amino-thiophenols.



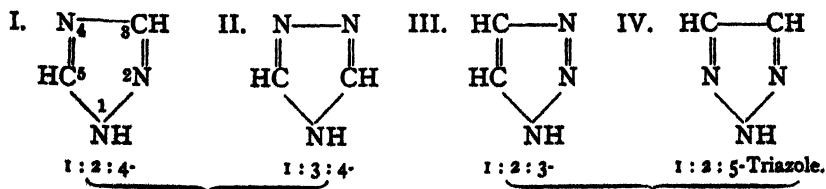
Certain derivatives of this group are of value as substantive cotton dyes. Thus when *p*-toluidine and sulphur are heated together for a considerable time at 200°, a product known as "**primuline base**" is obtained, containing the following thiazole derivative,



This is readily sulphonated to give **primuline**, which dyes cotton a yellow colour without the aid of mordants.

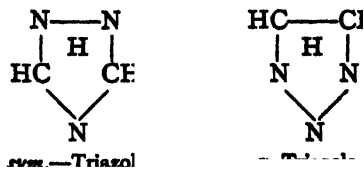
IV. TRIAZOLES

If two of the CH-groups in pyrrole are replaced by two N-atoms, four different ring systems may be derived, as represented by the following formulæ:

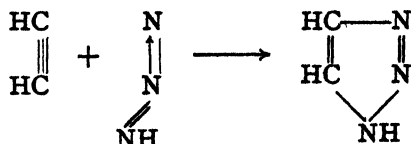


¹ H. Erlenmeyer and co-workers, *Helv. Chim. Acta*, 1938, 21, 863, 1017.

In this series we meet with tautomeric phenomena recalling those described under pyrazole (see pp. 693 *et seq.*). Whereas all four compounds are known in the form of their N-alkyl and N-acyl derivatives, the parent substance I appears to be identical with II, and similarly III and IV. For this reason it is sometimes convenient to make use of the following formulæ :



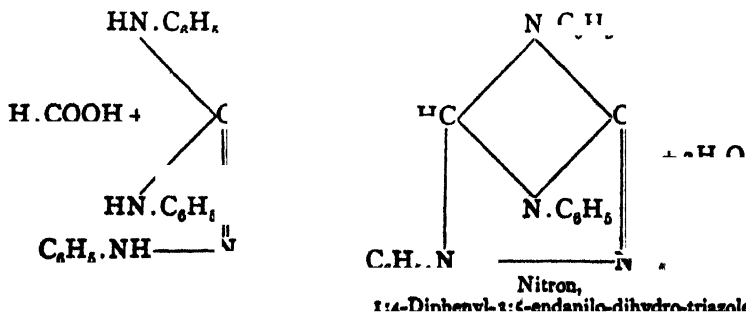
Many methods are used for the preparation of the triazoles, amongst which may be mentioned the addition of aliphatic diazo compounds (*e.g.* diazomethane) or azides (*e.g.* hydrazoic acid) to double or triple bonds. 1 : 2 : 3-Triazole, for example, is formed by the union of acetylene and hydrazoic acid.



The triazoles closely resemble the pyrazoles in behaviour, but are even more stable towards oxidising agents. They are very weak bases, although the introduction of two methyl or ethyl groups somewhat increases the basic strength.

Endimino-triazoles

Peculiar triazole bases with "nitrogen bridge" formulæ and known as endimino-triazoles were prepared by Busch. Their preparation from triaryl-amino-guanidines is exemplified by the preparation of 1 : 4-diphenyl-endanilo-dihydro-triazole, commonly called **nitron**, from triphenyl-aminoguanidine and formic acid according to the following equation :



It crystallises in yellow plates which melt at 189° with decomposition.

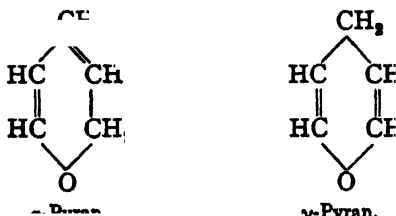
Endimino-triazoles are also of practical interest in so far as their nitrates are much more sparingly soluble than any other nitrates yet examined, so that these bases may be employed as a reagent for the nitrate ion.

The nitrate of 1:4-diphenyl-endanilo-dihydro-triazole is the least soluble of these compounds and may be used successfully for the *qualitative* and also the *quantitative estimation of nitric acid*. For this reason the base has been termed **nitron**.

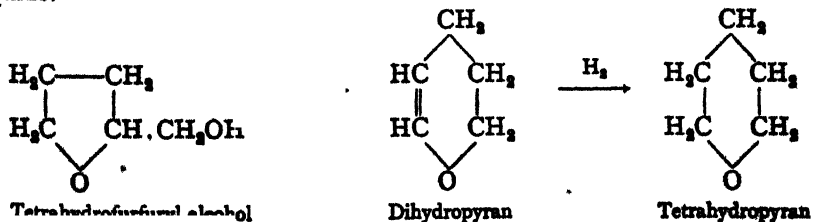
Schönberg¹ has pointed out that the structures advanced by Busch for the above compounds are very improbable owing to the distortion of the normal valency angles of the carbon joining the double bond to the four-membered ring. He suggests an inner salt formula for nitron.

IV Pyrans

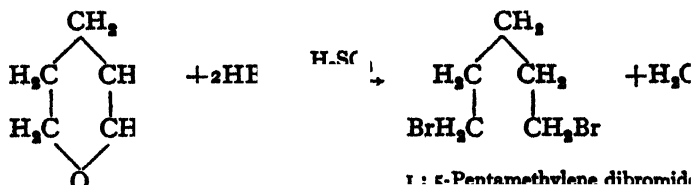
The simplest six-membered compounds with oxygen in the ring are the α - and γ -pyrans. Neither of these compounds nor their simple



derivatives are known, but *dihydro-pyran* and *tetrahydro-pyran* are readily obtained. When tetrahydro-furfuryl alcohol is passed over alumina at 300-400° *ring-enlargement* occurs with the formation of dihydropyran and this substance on reduction with hydrogen in the presence of Raney nickel gives tetrahydropyran. Both products are liquids.



Tetrahydropyran undergoes ring-fission when heated with hydrobromic and sulphuric acids, thus providing, incidentally, an excellent method for preparing 1 : 5-pentamethylene dibromide.

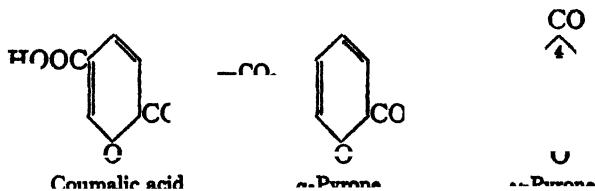


It will be noted that the presence of a divalent oxygen atom in the pyran ring precludes the possibility of an "aromatic" system of double bonds such as exists in benzene or pyridine. There are, however, salt-like derivatives called *pyrylium compound* in which the ring contains a conjugated system of three double bonds. The researches of Willstätter and Robinson showed that most of the pigments in flowers are pyrylium derivatives.

The most important pyran derivatives are the γ -pyrones which are the parent compounds of the flavones and possess the interesting property of forming crystalline salts with hydrochloric acid, picric acid, etc.

PYRONES¹

The pyrone ring contains five carbon atoms and one oxygen atom and according to their arrangement a distinction is drawn between the α -pyrones and γ -pyrones. The pyrone nucleus is found in a great variety of substances such as natural dyes and coloured compounds, alkaloids, fish poisons, insecticides, the hæmorrhagic clover compound, coumarins, etc. Many famous names—von Baeyer, Willstätter, W. H. Perkin, Jun., Robinson, Späth, and Karrer to mention a few—are associated with research in this field.



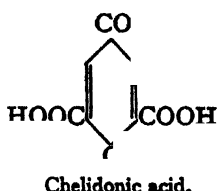
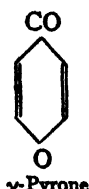
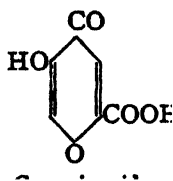
Benzo-derivatives of α -pyrone have already been described on p. 539 under coumarins, the γ -lactones of unsaturated *o*-hydroxycinnamic acids. A simple derivative is *coumalic acid* (coumalinic acid) which on decarboxylation by distillation of the mercury salt gives α -pyrone. The γ -pyrones, however, are more important and will be described in the following pages.

¹ *The Chemistry of the Monocyclic α - and γ -Pyrone*, L. F. Cavalieri, *Chem. Rev.*, 1947, 41, 525.

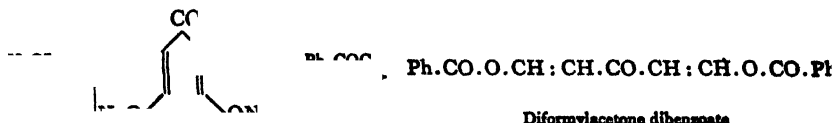
γ -Pyrones

γ -Pyrone, as already mentioned, is the parent compound of a series of substances found in nature, e.g. *brasilin*, the colouring matter of red-wood, *meconic acid* in opium, *chelidonic acid* in celandine and white hellebore, etc. γ -Pyrone derivatives are of interest in connection with investigations on the basic properties of oxygen.

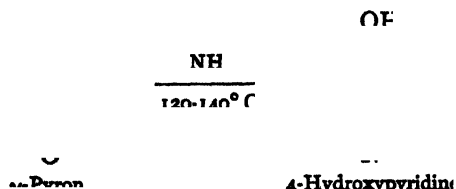
γ -Pyrone (needles, m.p. 32.5°) is prepared by the dry distillation of chelidonic acid or comenic acid (see p. 706) preferably with the addition of copper powder. The process obviously is one of decarboxylation.



The structure of the γ -pyrones is revealed not only by synthesis, but also by their reactions, particularly hydrolytic ring-fission with alkali and conversion into pyridones by means of ammonia. For example, brief treatment of γ -pyrone with cold alkali results in opening of the ring with the formation of diformyl-acetone (isolated as the dibenzoyl derivative by adding benzoyl chloride to the alkaline liquid). The



1:4-positions of the carbonyl and ethereal oxygen atoms are confirmed by the formation of 4-hydroxypyridine by heating γ -pyrone with ammonia at $120-140^\circ$



The close relationship between the pyrone and pyridine series suggests that various alkaloids derived from pyridine are in fact synthesised from pyrones in a manner similar to that just described. This hypothesis is strengthened by the occurrence of pyrone derivatives such as meconic acid (see next page) with the opium alkaloids.

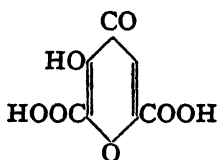


The γ -pyrone ring has a stability comparable to that of benzene. It is not attacked by the ordinary reducing agents or by nitric or sulphuric acid. With these acids it forms *pyronium salts*, and it is the presence of the resulting positive pole which makes the compound resistant to attack. The formation of these oxonium salts is discussed on p. 708.

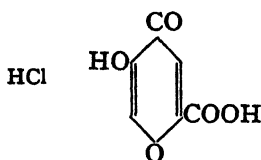
The ketonic properties which might be expected in γ -pyrone are completely absent: no hydrazones or oximes have been isolated and reducing agents, as already mentioned, have no effect.

Derivatives of γ -Pyrone

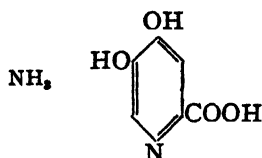
Naturally occurring γ -pyrone derivatives include *meconic acid* and *chelidonic acid*.



Meconic acid
3-Hydroxy- γ -pyrone-
2:6-dicarboxylic acid



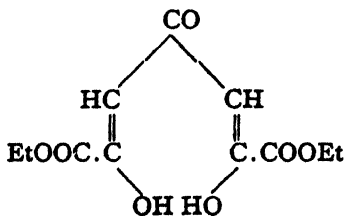
Comenic acid
5-Hydroxy- γ -pyrone-
2-carboxylic acid



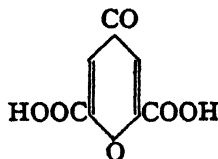
4:5-Dihydroxypyridine
2-carboxylic acid.

Meconic acid is present in opium and its structure is determined by synthesis. On decarboxylation by boiling with hydrochloric acid until one molecule of carbon dioxide is lost it gives *comenic acid*, whose structure is that given above. Obviously carbon dioxide might have been lost in a different manner to give the 3-hydroxy-2-carboxylic acid, but the structure assigned is correct since comenic acid couples with diazonium compounds thus showing the presence of a $\text{C}(\text{OH})=\text{CH}$ fragment in the molecule, and is converted on heating with ammonia to 4:5-dihydroxypyridine-2-carboxylic acid.

Another substance of the same type is *chelidonic acid*, found in the celandine and white hellebore. Its structure is based on its synthesis from acetone-dioxalic ester, which loses water—even when merely boiled in alcoholic solution—to form chelidonic ester. When acetone-dioxalic ester is heated with hydrochloric acid, loss of water and hydrolysis take place simultaneously with the direct production of chelidonic acid.



Acetone-dioxalic ester
(enolic form)



Chelidonic acid.

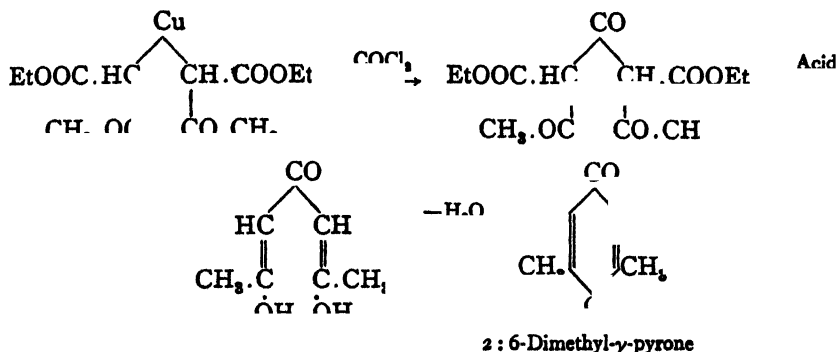
Like pyrone, chelidonic acid is readily disrupted to give open-chain compounds. On being boiled with alkali, it decomposes smoothly into 1 mol. acetone and 2 mols. oxalic acid.



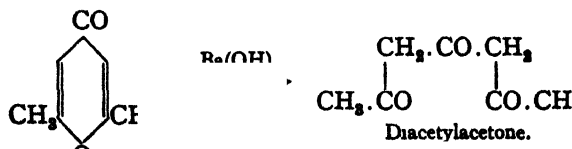
This confirms the structure of the acid.

Salt Formation of the γ -Pyrones and the Tetravalency of Oxygen

2:6-Dimethyl- γ -pyrone, m.p. 132° and b.p. 248° , was used by Collie and Tickle as the basis of an investigation into the tetravalency of oxygen. It is prepared by condensing the copper salt of acetoacetic ester with phosgene and boiling the product with sulphuric or hydrochloric acid. This is essentially a "ketonic hydrolysis" (see p. 281).

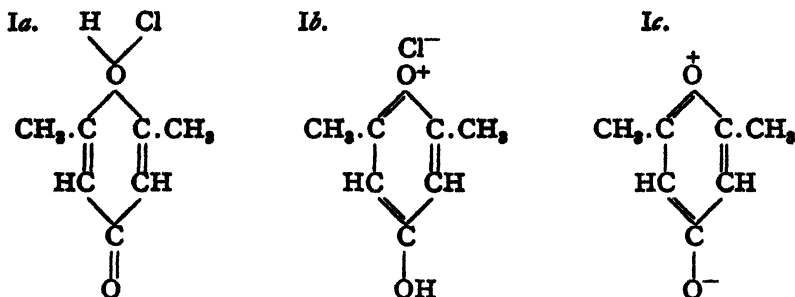


The ring is readily opened by heating with barium hydroxide with the formation of diacetylacetone.

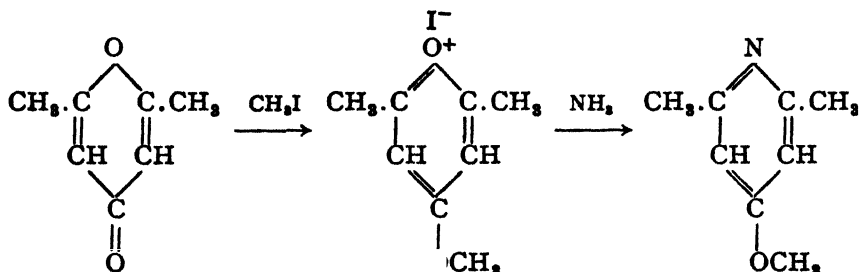


In the research quoted above, Collie and Tickle showed that dimethylpyrone forms addition products with a number of acids, such as $C_7H_8O_3$, HCl with hydrochloric acid; $(C_7H_8O_3)_2$, H_2PtCl_6 with hydrochloroplatinic acid; and $(C_7H_8O_3)_3$, $C_4H_6O_6$ with tartaric acid. It will be seen that these all result from the direct addition of acid, without loss of water. These **oxonium salts** are well-defined compounds, whose stability and behaviour can be explained on the assumption of a "tetravalent" oxygen atom with basic properties. It will be seen that

dimethylpyrone contains two oxygen atoms, leading to the possibility of either of the formulæ Ia or Ib for dimethylpyrone salts.



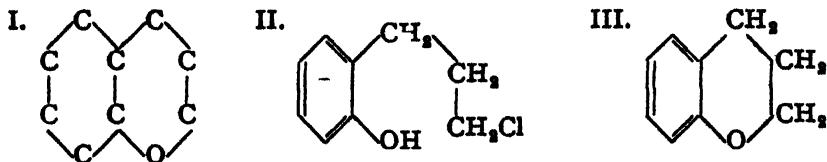
There is considerable evidence in favour of structure Ib, which may be regarded as formed from the betaine form (Ic) of the pyrone and hydrochloric acid. For example, methyl iodide adds on to dimethylpyrone and the resulting compound then reacts under very mild conditions with ammonia to give 2:6-dimethyl-4-methoxypyridine. This reaction is most simply explained by postulating the formation of a compound of type Ib.



An examination of the electrical conductivity of dimethyl-pyrone salts in aqueous solution indicates that they are almost completely hydrolysed.

Benzo Derivatives of γ -Pyrone

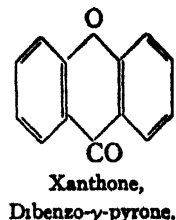
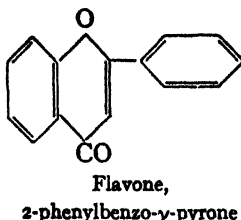
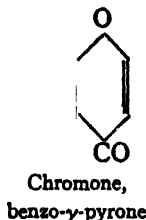
The cyclic oxide chroman (formula III below) may be regarded as the parent compound of a number of derivatives such as the chromones and coumarins, containing the atomic framework (I). Chroman has been



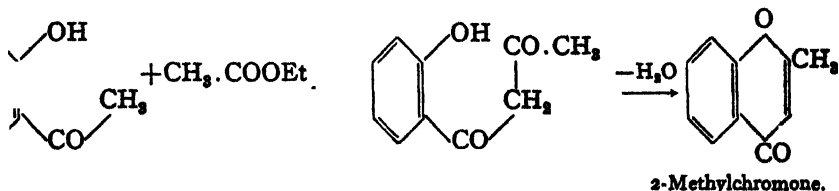
prepared from the base tetrahydroquinoline (see p. 727). The nitrogen ring of the latter may be opened to give *o*- γ -chloropropyl-aniline, which by means of the diazo-reaction can be converted into *o*- γ -chloropropyl-phenol (II). In alkaline solution this is quantitatively transformed into chroman.

Chroman is a strongly refractive liquid, which smells like peppermint and boils at 214° to 215° (749 mm. press.). It dissolves in concentrated sulphuric acid, giving a pink solution. The most important chroman derivatives are the tocopherols (vitamin E).

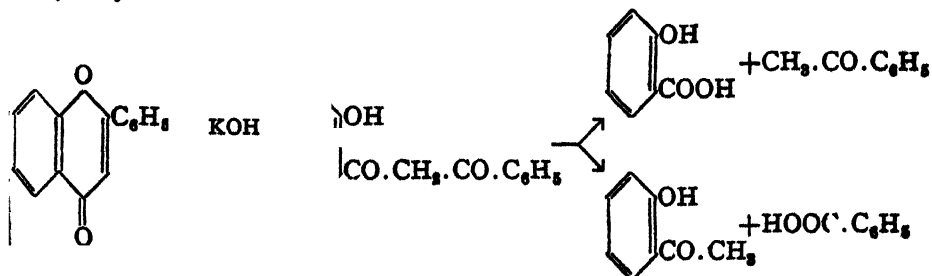
A number of benzpyrone derivatives, **chromone**, **flavone**, and **xanthone** give rise to naturally occurring yellow dyes and will be briefly described.



Chromones are synthesised by a number of methods involving the ring-closure of *o*-hydroxyacetophenone derivatives. For example, *o*-hydroxyacetophenone condenses in presence of sodium with fatty acid esters to give diketones, which undergo ring-closure with concentrated mineral acids. The product is 2-methylchromone.



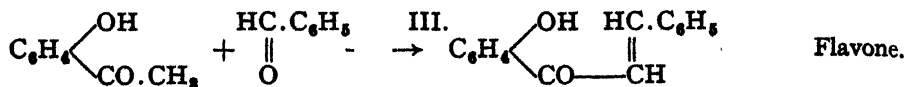
The reverse process occurs when chromones are boiled with alkali. The heterocyclic ring is broken and a diketone is formed which is readily disrupted further, since the diketone undergoes both "ketonic" and "acid" hydrolysis. Thus flavone, 2-phenylchromone, with 30 per cent. potassium hydroxide yields salicylic acid and acetophenone by "acid hydrolysis" and *o*-hydroxyacetophenone and benzoic acid by "ketonic hydrolysis."



This method is utilised in structural determinations.

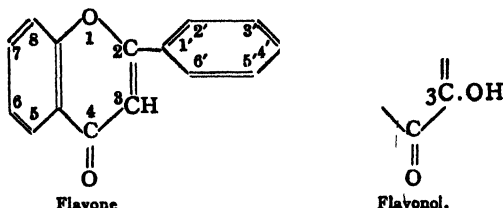
Flavone, m.p. 99° to 100° , is prepared in various ways, e.g. *o*-hydroxyacetophenone condenses with benzaldehyde to give hydroxy-chalcone

(III), which when acetylated and converted into the di-bromide yields flavone on subsequent treatment with alcoholic potash.



In this manner Kostanecki and his co-workers synthesised many naturally occurring flavone pigments. **Chrysin**, 5 : 7-dihydroxy-flavone, was the first of these pigments to be synthesised.

Position isomerides are described according to the following notation.



3-Hydroxyflavone is known as *flavonol*.

The yellow colour of many flowers is due to hydroxyflavones or hydroxyflavonols, representatives of which are given below. The hydroxyl groups may be alkylated or combined with sugar residues to form glycosidic linkages. There is evidence that flavones are precursors of anthocyanins.

Chrysin, 5 : 7-dihydroxyflavone, $\text{C}_{15}\text{H}_{10}\text{O}_4$, a constituent of poplar buds.

Luteolin, 5 : 7 : 3' : 4'-tetrahydroxyflavone, $\text{C}_{15}\text{H}_{12}\text{O}_6$, the dye of *dyer's weed*, *Reseda luteola*. It is said to be the oldest European dyestuff.

Fisetin, 7 : 3' : 4'-trihydroxyflavonol, $\text{C}_{15}\text{H}_{10}\text{O}_6$, isomeric with luteolin.

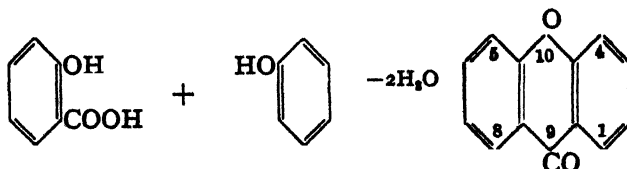
Quercetin, 5 : 7 : 3' : 4'-tetrahydroxyflavonol, $\text{C}_{15}\text{H}_{10}\text{O}_7$, a hydrolytic product of the 3-rhamnoside quercitrin $\text{C}_{21}\text{H}_{20}\text{O}_{11}$, present in the bloom of horse-chestnut.

Rhamnetin, methyl-quercetin, a hydrolysis product of the glycoside **xantho-rhamnin** contained in Avignon and buckthorn berries, is 3 : 5 : 3' : 4'-tetrahydroxy-7-methoxyflavone.

Morin, 5 : 7 : 2' : 4'-tetrahydroxyflavonol, is a constituent of the wood of *Morus tinctoria* ("fustic").

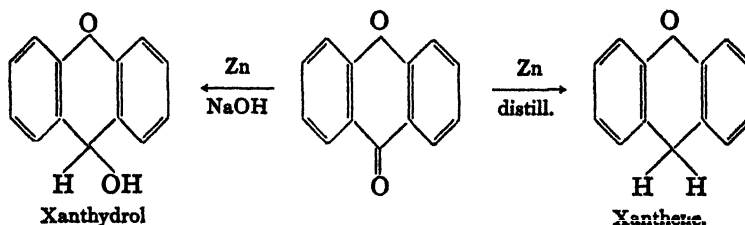
Apigenin, 5 : 7 : 4'-trihydroxyflavone, $\text{C}_{15}\text{H}_{10}\text{O}_5$, is obtained by the hydrolysis of the glycoside **apiin**, which occurs in parsley and to a smaller extent in celery.

The dibenzo-derivative of γ -pyrone is **xanthone**, m.p. 174° , which can be prepared by heating a mixture of salicylic acid and phenol with acetic anhydride which acts as a dehydrating agent.



It is a derivative of xanthene, into which it is converted by hydriodic acid and from which it is regenerated by oxidation with chromic acid. The

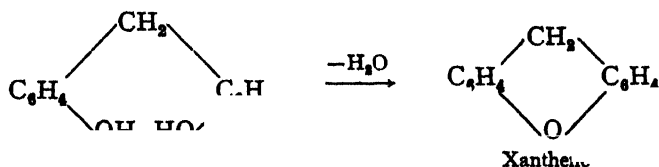
structure of xanthone is established by fusion with potassium hydroxide to yield 2 : 2'-dihydroxybenzophenone. Xanthone gives a brilliant blue fluorescence in concentrated sulphuric acid. In some respects it behaves as a typical ketone, giving on reduction with zinc dust and alkali the secondary alcohol xanthidrol and with zinc dust distillation or the Clemmensen method the parent compound xanthene.



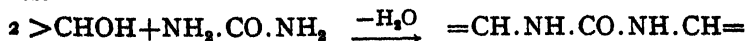
On the other hand xanthone is insensitive towards ketonic reagents such as hydroxylamine and reacts with these only under forcing conditions.

A naturally occurring xanthone derivative is **euxanthone**, 1:7-dihydroxyxanthone, which occurs as the glucuronic acid derivative, *euxanthic acid*, in the dye-stuff Indian Yellow. As is often observed in compounds of this type the 1-hydroxyl group adjacent to the carbonyl group is much less reactive than other hydroxyl groups in the molecule. This is shown by the formation of 7-methoxy-1-hydroxyxanthone when euxanthone is methylated by methyl iodide and potassium hydroxide. There can be little doubt that the 1-hydroxyl group is chelated with the carbonyl group.

Xanthene, m.p. 100°, prepared as already stated by reduction of xanthone, can be synthesised by heating 2:2'-dihydroxydiphenylmethane. Its structure is thus established.



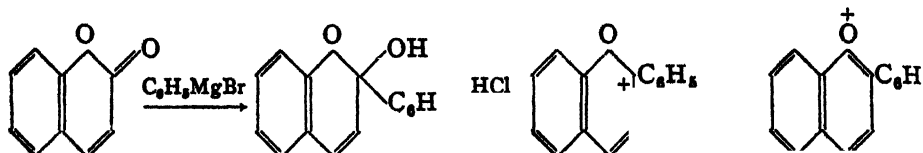
Another reduction product of xanthone is **xanthinol** (see above). The hydroxyl group in this compound is very reactive. For instance it reacts with ureas to give products which may be used for identification purposes.



Pyrilium Salts

As already mentioned, pyrones, chromones, and xanthenes can attain full aromaticity only in the form of pyrylium salts. This is shown by 2-phenylchromylium or flavylium chloride. Coumarin with phenylmagnesium bromide yields 2-phenylchromenol, which reacts with hydro-

chloric acid to give flavylum chloride. This salt is a resonance hybrid in which the principal forms are carbonium and oxonium salts.



These salts are to be distinguished from the oxonium salts such as those of ether and γ -pyrone, which contain a hydrogen atom coordinated to an oxygen atom and are unstable. The pyrylium salts contain no such hydrogen atom and are stable. They are of great importance since the naturally occurring pigments known as the anthocyanins (p. 833) are hydroxyflavylum salts.

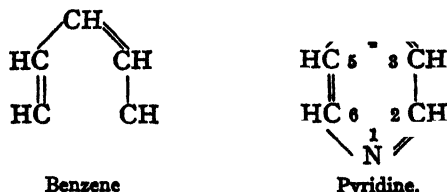
Xanthydrol with hydrochloric acid similarly forms xanthylum salts.

V

Pyridine Group

PYRIDINE ¹

Pyridine and its derivatives contain a ring composed of five carbon atoms and one nitrogen atom. Pyridine can therefore be derived from benzene by replacing a trivalent CH-group by an atom of nitrogen.



The above formula, proposed independently by Körner in 1869 and Dewar in 1871, has been preferred to other formulæ which have been advanced, since it offers a satisfactory explanation of the chemical behaviour of pyridine and its derivatives. It has been confirmed both by synthesis and by the relationship of pyridine to piperidine (p. 720).

The possibilities of isomerism among pyridine derivatives are greater than with benzene, since not only does the relative position of the constituents to one another enter into the question, but also their position with regard to the nitrogen in the ring. The prediction of the existence

¹ *The Chemistry of the Pyridines* by H. S. Mosher in *Heterocyclic Compounds* (Editor, R. C. Elderfield), vol. I, p. 397. *Pyridine, Quinoline and Isoquinoline*, by F. W. Bergstrom, *Chem. Rev.*, 1938, 52, 397.

of three monosubstitution products and six or twelve disubstitution products, according as the substituents are similar or dissimilar, has been completely borne out by experiment.

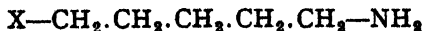
Preparation, Properties and Uses of Pyridine.—Pyridine and certain of its homologues are produced by the action of heat on coal, peat, wood and various bituminous shales, and are thus present in the tar obtained by the dry distillation of these substances. They also occur in the unpleasant smelling product known as Dippel's oil, formed by the dry distillation of bones from which the fat has not been extracted. As will be seen later, pyridine results from various alkaloids by the action of heat or alkalis, or by distillation with zinc dust at a red heat.

The chief source of pyridine and its homologues is coal tar. The fraction of the tar boiling between 80° and 170° ("light oil," see p. 428) used for the production of benzol is also worked up for pyridine bases, which are present to the extent of several units per cent. The oil is washed with dilute sulphuric acid in lead-lined vessels, and the bases are then liberated from the acid solution by addition of lime, and purified by rectification. The mixture of pyridine bases so obtained is used industrially in denaturing spirits, as a solvent for acylations with acyl chlorides, and pyridine itself is used in the preparation of pharmaceuticals such as sulphapyridine (p. 869).

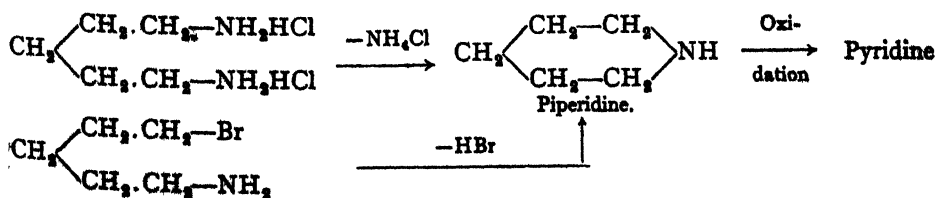
Pyridine is a colourless liquid of unpleasant, penetrating smell, b.p. 115° . It is miscible in all proportions with water, alcohol, and ether, and forms salts with acids. Among the latter the picrate and perchlorate are difficultly soluble and are used for the isolation and purification of pyridine. Pyridine may also be detected by the formation of "*photopyridine*" by exposure to ultra-violet light. The "photopyridine" thus formed gives intense colours with primary amines. The chemical properties of pyridine are discussed on p. 715.

Syntheses of Pyridine and its Derivatives

1. The simplest method of building up a pyridine ring is from aliphatic compounds of the general formula



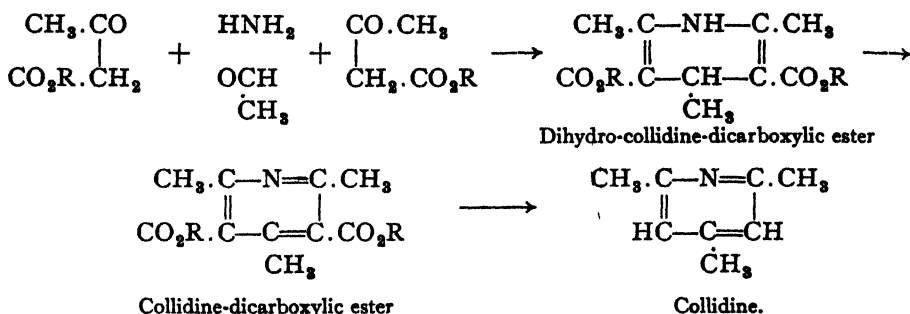
which may be converted into piperidine by ring formation, and by subsequent oxidation yield pyridine. Thus pentamethylene-diamine hydrochloride, on rapid heating, decomposes into ammonium chloride and



piperidine. Similarly, normal ω -chloro- and ω -bromo-amylamine lose hydrogen halide on heating with alkali to give piperidine (Ladenburg).

These syntheses prove the constitution of piperidine and pyridine.

2. A synthesis of general application is due to Hantzsch. Aldehyde-ammonia unites with acetoacetic ester to form *dihydro-collidine-dicarboxylic ester*, which under the influence of nitrous acid loses two hydrogen atoms and is transformed into *collidine-dicarboxylic ester*. From this, by hydrolysis and elimination of carbon dioxide, *collidine* (*s*-trimethyl-pyridine) is obtained.



It may be assumed that one molecule of aldehyde-ammonia (or aldehyde and ammonia) reacts with two molecules of acetoacetic ester, to form an alkylidene-acetoacetic ester and β -amino-crotonic ester, and that these compounds then interact with the production of a dihydropyridine derivative. In confirmation of this, it has been shown that by working at low temperatures, at which the formation of dihydropyridine derivatives is retarded, the presence of alkylidene-acetoacetic ester can be proved.

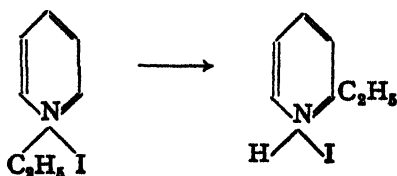
The above reaction may be varied by using other aldehydes in place of acetaldehyde, and other 1:3-diketones, such as acetylacetone or benzoyl-acetone, instead of the second molecule of acetoacetic ester.

Other reactions have been developed which permit a further extension of the above synthesis. Among these are the formation of dihydropyridine derivatives by condensing 1:5-diketones with ammonia, and alkylidene-acetoacetic esters with β -amino-crotonic ester or ammonia derivatives of 1:3-diketones. Alkylidene-malonic esters may also be employed in place of alkylidene-acetoacetic esters in the synthesis of pyridine compounds.

3. The intramolecular rearrangement of the alkylidides, which has already been described in the cases of aniline (p. 468), pyrrole (p. 659) and pyrazole (p. 691), was observed by Ladenburg in the pyridine group, and offers a general means of converting pyridine into its homologues. As a tertiary base pyridine unites with alkyl iodides to form the corresponding ammonium iodides. When these are heated under pressure the alkyl radical migrates from nitrogen to a carbon atom of the nucleus,

assuming either the 2- or 4-position with respect to nitrogen, but never the β -position.

Thus pyridine ethiodide yields the hydriodide of ethylpyridine :



Examples of other methods of preparing pyridine derivatives are to be found on pp. 661 and 706.

General Behaviour of Pyridine Derivatives.—The parent compound and its homologues are weak bases—pyridine, pK_a 5.23, *cf.* aniline 4.47—which unite with one equivalent of acids to form salts and combine with inorganic salts such as mercuric chloride to give double salts of the type $C_5H_5N, HgCl_2$ and $(C_5H_5N)_2, (HgCl_2)_3$. As tertiary bases they combine with alkyl halides to give quaternary ammonium salts, pyridine with methyl iodide forming *N-methylpyridinium iodide*. The methiodides and certain salts of pyridine and quinoline exist in modifications of different colour. The polychromism of these derivatives is ascribed to **chromo-isomerism**.¹

The strong resemblance between the pyridine and benzene series is emphasised by the following facts. Both are characterised by their great stability, benzene having a resonance energy of 39 Kcal./mole and pyridine 43 Kcal./mole. Like benzene pyridine is unattacked by many oxidising agents, but unlike benzene it is oxidised by acid or alkaline potassium permanganate.² In consequence while potassium permanganate converts pyridine homologues into carboxylic acids in the same manner as benzene homologues, the yields are frequently poor since nuclear as well as side-chain oxidation occurs. From the constitution of the pyridine acids so obtained conclusions may be drawn as to the number and position of the side-chains originally present. The stability of the pyridine ring is further stressed by the oxidation of the phenylpyridines to pyridine-carboxylic acids, the pyridine ring remaining intact while the benzene nucleus is destroyed. In quinoline, too, it is the benzene ring which is oxidised although in *isoquinoline* both the benzene and the pyridine rings are susceptible to oxidation.

There are, however, notable differences between pyridine and benzene, as indeed is to be anticipated from a consideration of the fine structure of pyridine. The nitrogen atom in pyridine has an attraction for electrons, which results in a general lowering of the electron density on all the carbon atoms and particularly at C_2 and C_4 by electromeric change. In other words pyridine is a resonating compound with main contributing

¹ A. Hantzsch and O. K. Hofmann, *Ber.*, 1911, 44, 1776, 1783.
rend., 1927, 284, 206. B. D. Shaw and A. L. Wilkie, *J.*, 1928, 1377.

M. Delépine, *Compt.*

forms such as I and minor contributions from the polar forms II and III.



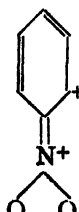
(II)

(III)

Two consequences follow from this picture of the pyridine molecule. (1) Pyridine will be resistant to electrophilic substitution and such substitution will occur in the 3- and 5-positions. In practice it is found that halogenation, nitration, and sulphonation occur only under severe conditions and afford 3-monosubstituted products. It is noteworthy that at 300° 3-bromopyridine is formed by the action of bromine on pyridine and at a still higher temperature (500° C.) 2-bromopyridine is obtained.¹ It is probable that this difference is due to bromination at the lower temperature occurring by ionic attack and at the higher temperature by free radical attack.

(2) Pyridine and its derivatives will be susceptible to nucleophilic attack at the 2- and 4-positions. This in fact is found to be so. Sodamide in xylene gives 2-aminopyridine and continued action yields 2:6-diaminopyridine (p. 718). The point of attack reflects the nucleophilic character of the entering substituent (—NH_2).

The strongly negative character of the nitrogen atom is clearly similar to that of the nitro-group and it is accordingly to be expected that pyridine and its derivatives will resemble nitrobenzene and its derivatives. This is strikingly shown by the halogen mobility of the 2- and 4-halogenopyridines (*cf.* *o*- and *p*-chloronitrobenzenes, p. 466). For example, 2-



and 4-chloropyridines with ammonia yield 2- and 4-aminopyridine in contrast to the 3-chloropyridine which requires a copper catalyst. The reaction is essentially an attack by the NH_3 anion at the electron deficient C_2 atom.

The 2- and 4-methyl-pyridines are also unusually reactive. According to experimental conditions they either condense with aldehydes to form products of the aldol type known as *alkines*, *e.g.* compound I, or else water is eliminated and oxygen-free, unsaturated bases, such as 2-allyl-

¹ J. P. Wibaut and H. J. den Hertog, *Rec. Trav. Chim.*, 1932, 51, 381. S. M. McElvain and M. A. Goese, *J.A.C.S.*, 1943, 65, 2227.

pyridine (II), are produced. The latter are generally termed *stilbasoles*. As will be seen later, the 2-allyl-pyridine obtained by this reaction is an intermediate product in the synthesis of the alkaloid coniine. Phthalic anhydride and phthalimide may also be employed in place of aldehydes in this condensation

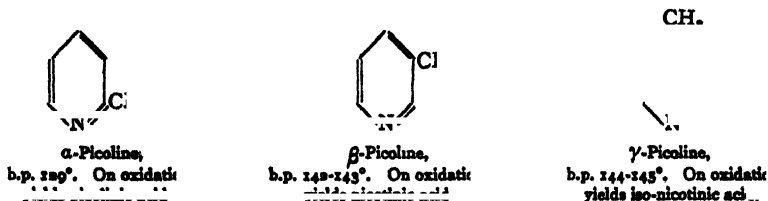


The reactivity of the methyl groups in the 2- and 4-positions of pyridine is greatly increased by conversion of the pyridine into the quaternary salts. This is strikingly shown by the inertness of 2-picoline towards *p*-nitrosodimethylaniline, whereas the methiodide condenses readily in the presence of piperidine. 2-Picoline condenses with aldehydes as mentioned above, but only under vigorous conditions. The methiodide on the other hand reacts very readily.¹

On reducing pyridine bases with sodium and alcohol, six atoms of hydrogen are taken up with formation of piperidine bases. More energetic reduction, by heating with hydrogen iodide, ruptures the ring with the production of paraffins, *e.g.* pyridine is converted into pentane.

Homologues of Pyridine.—The alkyl derivatives of pyridine mentioned above are found together with pyridine itself in bone oil and coal tar.

Methylpyridines or Picolines, C₆H₇N. All three possible isomerides are known. They may be isolated from coal tar, or synthesised by the methods quoted above. The β -isomer is used in great quantities in the manufacture of the vitamin, nicotinic acid.

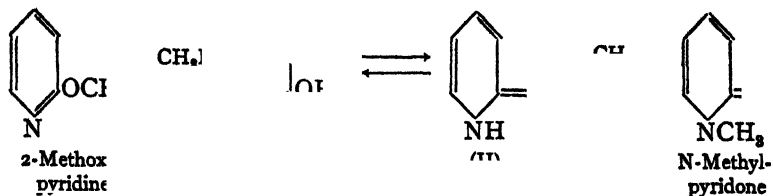


Lutidines, C₇H₉N. Nine isomerides are theoretically possible, three ethyl-pyridines and six dimethyl-pyridines. Of these, the three ethyl and five of the dimethyl-derivatives are known.

Hydroxypyridines or Pyridones.—The three hydroxypyridines are substances which crystallise well and are best prepared by the decarboxylation of the readily available corresponding carboxylic acids (p. 706). As the names imply, tautomerism is observed in the hydroxypyridine series. 3-Hydroxypyridine reacts entirely as a phenol, but the 2- and 4-isomers react both as true hydroxy-compounds containing a phenolic hydroxyl group, and as ketonic derivative of a dihydropyridine, *i.e.* as

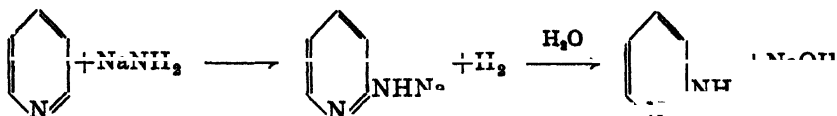
¹ C. F. Koelsch, *J.A.C.S.*, 1944, 66, 8126. A. P. Phillips, *J. Org. Chem.*, 1947, 12, 333.

a pyridone. In other words these two compounds exhibit lactam-lactim tautomerism, the 2-compound, for instance, reacting in the lactim form as 2-hydroxypyridine (I) and in the lactam form as 2-pyridone (II). Chemical evidence for both forms is furnished by methylation, methyl iodide yielding N-methyl-2-pyridone and diazomethane giving 2-methoxypyridine.

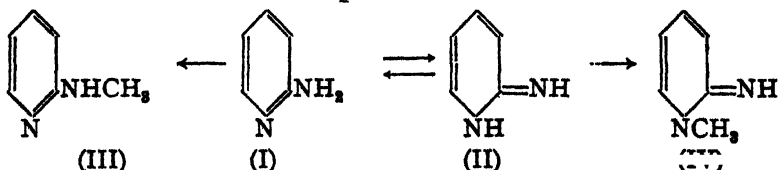


The ultra-violet spectrum of 2-hydroxypyridine closely resembles that of N-methyl-2-pyridone and differs from that of 2-methoxypyridine. Since methyl groups do not migrate under ordinary conditions the constitution of the two methyl compounds is "fixed", and it follows that in neutral solution 2-hydroxypyridine has the pyridone structure.

Aminopyridines.—As already stated the aminopyridines can be obtained by the amination of the bromo- or chloro-pyridines. 2-Aminopyridine, however, is obtained most easily by the direct amination of pyridine with sodamide (p. 716). This reaction, which was discovered by Tschitschibabin, is of great value in the preparation of 2-amino-derivatives of the pyridine and the quinoline series.¹



3-Aminopyridine has the properties of an aromatic primary amine and is readily diazotised. The 2- and 4-aminopyridines on the other hand do not undergo normal diazotisation, and they differ in other respects from the 3-isomer. This is illustrated by the fact that 2- and 4-aminopyridine give rise to two series of derivatives and behave tautomerically in the amino-form (I) or the imino-form (II). As with the hydroxypyridines this tautomerism is convincingly shown by methylation. Sodio 2-aminopyridine with methyl iodide yields mainly 2-methylaminopyridine (III), while the free base with methyl iodide and silver oxide gives almost entirely N-methyl-2-pyridone-imide (IV).

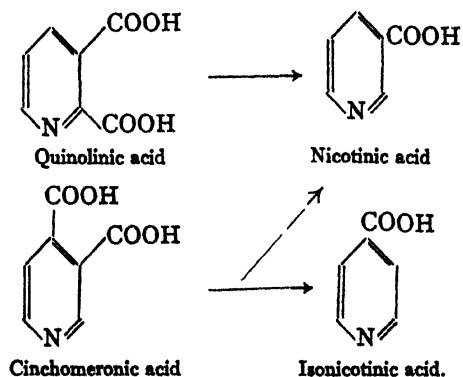


¹ M. T. Leffler gives a general account of the reaction in *Organic Reactions* (edited by Roger Adams), i. 91.

As often happens in the study of tautomerism ultra-violet spectroscopy yields further insight into the tautomerism of the aminopyridines. The ultra-violet spectrum of 2-aminopyridine closely resembles that of pyridine and 2-dimethylaminopyridine and differs considerably from that of 1-methyl-2-pyridoneimide. The same applies to 4-aminopyridine and its corresponding derivatives. It is therefore clear that these amines in neutral solution exist in the amino-form.

Pyridine-carboxylic acids.—Carboxylic acids of the pyridine series result, as stated above, from the oxidation of pyridine derivatives containing organic side-chains. Hence they are frequently obtained as degradation products of vegetable alkaloids and quinoline derivatives, and a knowledge of their constitution is of great value in the orientation of these heterocyclic compounds. They are solids, which possess both acidic and basic character, although the basic properties are not very evident in poly-carboxylic acids. The 2-acids are very readily decarboxylated. The 4-acids lose carbon dioxide less readily and the 3-acids still more reluctantly. This is shown by quinolinic acid, pyridine-2 : 3-dicarboxylic acid, on heating giving nicotinic acid, pyridine-3-carboxylic acid; and pyridine-3 : 4-dicarboxylic acid gives mainly pyridine-3-carboxylic acid (see below). The same order is given by the decarboxylation of pyridine-2 : 3 : 4-tricarboxylic acid, which when heated at 180° affords pyridine-3 : 4-dicarboxylic acid. This acid is then decarboxylated at 220° to pyridine-3-carboxylic acid.

The pyridine mono-carboxylic acids are orientated as follows. Quinoline and isoquinoline on oxidation yield quinolinic acid and cinchomeronic acid respectively: the constitution of these acids is known from this method of preparation. Nicotinic acid is obtained by the partial decarboxylation of either acid, but isonicotinic acid from cinchomeronic acid only.



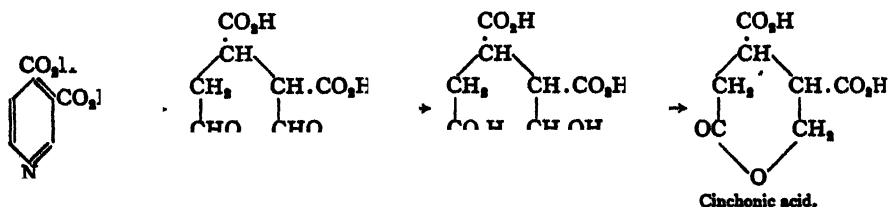
It is clear that nicotinic must be the 3-acid and isonicotinic the 4-acid. The remaining acid, picolinic acid, must therefore be the 2-acid. This proof of the structures of these acids is one of the foundations upon which the orientation of pyridine derivatives has been built.

Nicotinic acid, pyridine-3-carboxylic acid, m.p. 236° - 237° , has been obtained by oxidation of various alkaloids (*e.g.* nicotine, pilocarpine, hydrastine, berberine). It is best prepared either by oxidation of 3-picoline or from 3-bromopyridine by conversion into the nitrile by Rosenmund's method, followed by hydrolysis of the nitrile.¹ Nicotinic acid has been shown to be one of the components of the vitamin B group (see section on Vitamins).

Coramine, the diethylamide of pyridine-3-carboxylic acid, resembles camphor in many of its physiological properties. In some respects its action is more powerful than that of camphor, *e.g.* on the blood pressure and respiration, and as an antidote to morphine. Hence it is employed medicinally.

Isonicotinic acid hydrazide is finding use in the treatment of tuberculosis.

Quinolinic acid, 2:3-pyridine-dicarboxylic acid, is formed by the oxidation of quinoline with alkaline permanganate, from which its constitution follows. It may be prepared in very good yield by oxidising 8-hydroxy-quinoline with concentrated nitric acid. It melts at 192° , with evolution of carbon dioxide and conversion into nicotinic acid. **Cinchomeric acid, 3:4-pyridine-dicarboxylic acid**, is formed along with phthalic acid by the oxidation of isoquinoline, and this reaction determines its structure. It melts at 258° to 259° , with evolution of carbon dioxide to form a mixture of nicotinic and isonicotinic acids. An interesting example of ring-fission of the pyridine molecule is provided by the reduction of cinchomeric acid which yields the γ -pyrone derivative, **cinchonic acid**. The course of the reaction is shown in the scheme.



Reduction is accompanied by removal of the nitrogen and formation of a dialdehyde which undergoes the Cannizzaro reaction to give an intermediate containing three carboxyl and one alcoholic group. Loss of water results in ring-closure and formation of the pyrone.³

Piperidine.—Reduction of pyridine and its derivatives by means of sodium and ethanol yields hexahydro-compounds, 1:4-dihydropyridines being formed as intermediate products.⁴ **Piperidine, hexahydropyridine**, b.p. 105.6° , was first prepared from the alkaloid piperine, present in pepper, by heating with alkali. Its formation by synthetic methods and by the reduction of pyridine (with sodium and ethanol or by electrolytic means), has already been mentioned. Its close relationship to pyridine was recognised by Hofmann and established by Königs by the inter-conversion of the two substances. Whereas pyridine is a weak tertiary base of aromatic character, piperidine, as would be anticipated from its

¹ McElvain and Goese, *J.A.C.S.*, 1941, 63, 2283. ² E. Sucharda, *Ber.*, 1925, 58, 1727.

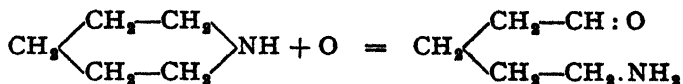
³ O. Mumm and K. Brodersen, *Ber.*, 1923, 56, 2295. ⁴ B. D. Shaw, *J.*, 1925, 215.

fully reduced ring-structure, is a strong secondary amine, pK_b 11.1, whose behaviour classes it with the aliphatic amines. It is a colourless liquid of peculiar ammoniacal smell, miscible in all proportions with water and ethanol. The imino-hydrogen may be acetylated or benzoylated, and with nitrous acid gives N-nitrosopiperidine. Piperidine is dehydrogenated to pyridine by concentrated sulphuric acid at 300° ; nitrobenzene at 250° ; or silver acetate at 180° . It is used extensively as a catalyst in reactions such as the Knoevenagel and Michael condensations.

Methods of Opening the Piperidine Ring

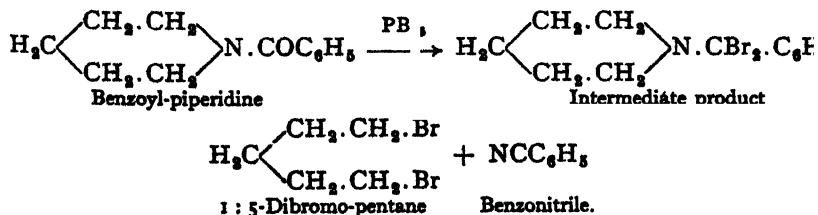
A number of methods are available for rupturing the piperidine ring, processes which are in a sense a reversal of the syntheses described on p. 713 *et seq.* These reactions are of great value in determining the structure of piperidine and its derivatives. They also throw light on the constitution of dehydrogenated piperidine, pyridine.

1. **By Oxidation.**—Under the influence of oxidising agents, such as hydrogen peroxide, the piperidine ring is comparatively easily broken between the nitrogen atom and an adjacent carbon atom, with the formation of δ -amino-valeraldehyde. Reduction of δ -aminovaleraldehyde with zinc and hydrochloric acid gives piperidine.



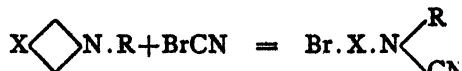
The opening of the ring is effected even more readily by the action of potassium permanganate on N-acylated piperidine derivatives. In this way benzoyl-piperidine, $\text{C}_5\text{H}_{10}\text{N}(\text{COC}_6\text{H}_5)$, yields benzoyl- δ -aminovaleric acid.

2. **By Means of Phosphorus Halides.**—The work of J. v. Braun showed that acyl derivatives of piperidine are very easily attacked by phosphorus pentachloride or pentabromide. Under chosen conditions the resulting 1 : 5-dichloro-pentane or 1 : 5-dibromo-pentane is obtained in so good a yield that the reaction can be used as a means of preparing these halogen compounds.



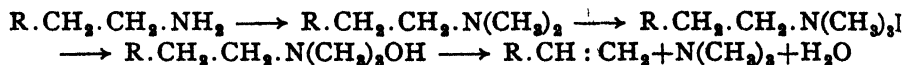
3. **By Means of Cyanogen Bromide.**—J. v. Braun has also discovered that substitution products of piperidine, and other cyclic tertiary bases of the general type $\text{X} \begin{array}{c} \diagup \quad \diagdown \\ \text{ } \end{array} \text{N} \cdot \text{R}$, are disrupted by cyanogen bromide

according to the following equation to give brominated cyanamide $\text{Br} \cdot \text{XN}(\text{CN}) \cdot \text{R}$,

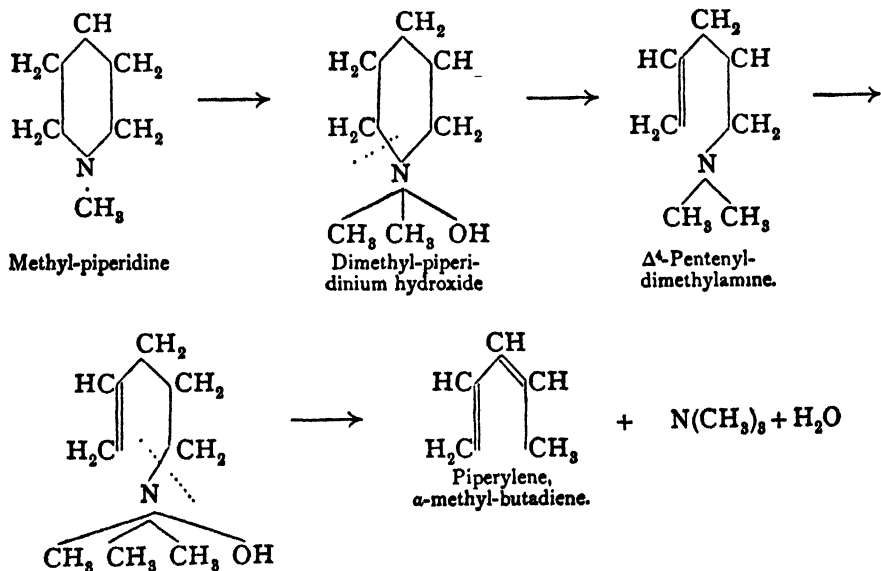


provided that the alkyl group R is not removed from the molecule. Such a cyanamide derivative may undergo hydrolysis to a brominated secondary amine, $\text{Br} \cdot \text{X} \cdot \text{NH} \cdot \text{R}$. This constitutes the simplest available method of opening a ring containing nitrogen, and may also be employed with success in cases where (as with the aromatic derivatives of piperidine) the following method (4) cannot be applied.

4. By Means of Exhaustive Methylation.—A method of opening the piperidine ring, with simultaneous loss of nitrogen, is by "exhaustive methylation." This is based on the observation that many quaternary ammonium hydroxides on distillation lose water to give an unsaturated hydrocarbon and a tertiary amine.



A similar series of reactions, first used by A. W. Hofmann in the case of piperidine, was correctly interpreted by Ladenburg and later applied by other investigators to a large number of cyclic bases (see p. 741). It has been the classical weapon of attack in determining the



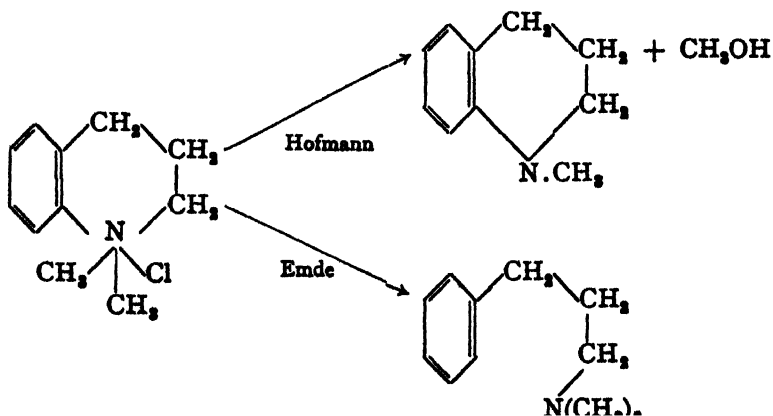
constitution of the majority of vegetable alkaloids, and may therefore be treated in some detail. The operations are as follows: Piperidine, as a secondary base, can be methylated at the nitrogen atom by means of methyl iodide. The methyl-piperidine so obtained unites with methyl iodide to form dimethyl-piperidinium iodide, and this by treatment with

moist silver oxide (or potassium hydroxide) is converted into dimethyl-piperidinium hydroxide. The latter on dry distillation breaks up into water and a compound frequently described as dimethyl-piperidine, but correctly named Δ^4 -pentenyl-dimethylamine. Being a tertiary base, this substance also unites with methyl iodide to form a substituted ammonium iodide, which when converted as before into the ammonium hydroxide and submitted to dry distillation yields trimethylamine, water, and a hydrocarbon, α -methyl-butadiene, of the formula C_5H_8 .

The addition product formed by Δ^4 -pentenyl-dimethylamine with hydrochloric acid readily isomerises into the methochloride of 1:2-dimethyl-pyrrolidine, thus forming a connection between the pyridine and pyrrole series.

It will be noted from the two examples given above that nitrogen is removed from an open-chain compound by a single distillation of the quaternary salt, while with the ring compound the process of methylation and distillation has to be repeated. Exhaustive methylation therefore not only gives information regarding the skeleton structure of heterocyclic compounds, but also shows whether the nitrogen is a member of a ring or open-chain.

5. By Emde's Method.—In some instances where the method of exhaustive methylation fails, the Emde method may be applied. This consists in treating a quaternary ammonium salt with sodium amalgam. The use of this method may be exemplified by N:N-dimethyl-tetrahydroquinolonium chloride. The Hofmann method fails to open the ring, the products being N-methyl-tetrahydroquinoline and methyl alcohol. On the other hand, the Emde method yields chiefly dimethylaminopropylbenzene.

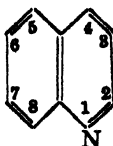


6. By Reduction.—When heated to 300° with hydriodic acid, piperidine decomposes into *n*-pentane and ammonia.

VI

Quinoline, Isoquinoline and Acridine Groups

Quinoline is related to pyridine in the same manner as naphthalene to benzene, and is 2 : 3-benzo-pyridine, or a naphthalene in which one CH-group in the α -position is replaced by a nitrogen atom.



In this series the number of *isomeric substitution products* is very large. A glance at the formula for quinoline reveals the fact that no two hydrogen atoms are similarly situated with respect to the nitrogen atom. The position of substituents is best represented by making use of the above numbering.

Quinoline¹

Quinoline, C_9H_7N , was first isolated in the impure state by Runge in 1834 from coal-tar and a little later (1842) by Gerhardt who distilled cinchonine with potassium hydroxide. It is a colourless, oily liquid which boils at 240° and solidifies at -19.5° . It possesses a characteristic smell, is almost insoluble in water, and dissolves readily in most organic solvents. In chemical properties it resembles pyridine and like the latter is a tertiary base. Commercial quinoline is manufactured synthetically.

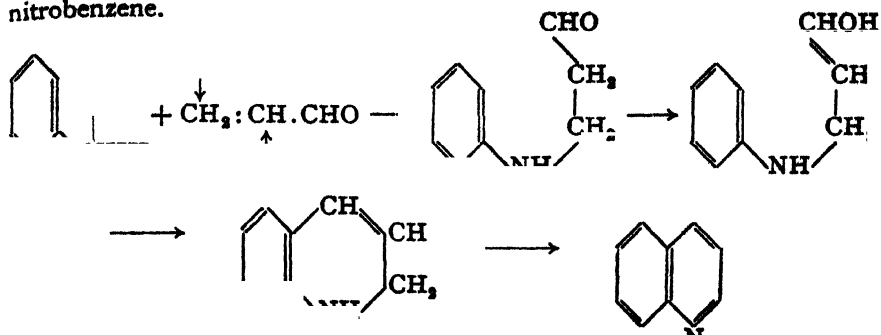
Syntheses. A considerable number of syntheses have been used to prepare quinoline and substituted quinolines. Of these three call for discussion: the syntheses of Skraup, Döbner and von Miller, and Friedländer.

(1) Preparations of quinoline and those derivatives substituted in the benzene nucleus are based almost exclusively on the *Skraup synthesis*, in which an aromatic primary amine is heated with glycerol and sulphuric acid in the presence of nitrobenzene or some other oxidising agent such as arsenic acid or the sodium salt of *m*-nitrobenzenesulphonic acid. Quinoline is obtained in this way by heating aniline, glycerol, and nitrobenzene with concentrated sulphuric acid.

The mechanism of the reaction is in all probability as follows: Under the dehydrating influence of sulphuric acid glycerol is first converted into acrolein; this condenses with aniline in the presence of the strong

¹ The Chemistry of Quinoline, R. H. Manake, *Chem. Reviews*, 1942, 30, 113.

acid to form β -phenylamino-propaldehyde, which loses water yielding a dihydroquinoline. The latter is then oxidised to quinoline by the nitrobenzene.



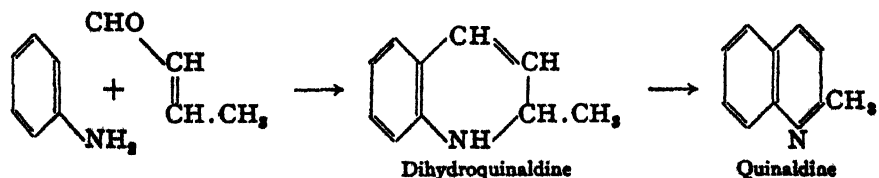
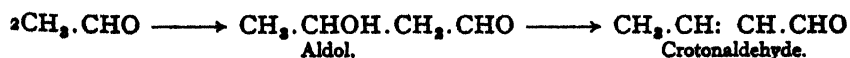
It was formerly assumed that the first stage in the synthesis was a condensation of aniline with acrolein to give the anil (Schiff's base), $\text{C}_6\text{H}_5.\text{N}:\text{CH}.\text{CH}:\text{CH}_2$, but this does not occur in the presence of a strongly hydrolysing agent such as sulphuric acid. The correctness of the mechanism given above is confirmed by the formation of 2-methylquinoline from aniline and crotonaldehyde.

The reaction has proved extraordinarily fruitful, since the place of aniline may be taken by substituted anilines thus enabling a great variety of quinoline derivatives containing substituents in the benzene ring to be prepared. In addition, aniline may be replaced by naphthylamines with the formation of naphthaquinolines; and by making use of diamines two pyridine rings may be linked on to the benzene nucleus, the compounds so obtained being known as *phenanthrolines*.

The preparation of Alizarin Blue described on p. 600, which was known before the discovery of Skraup's synthesis, is another example of this method of forming a quinoline derivative.

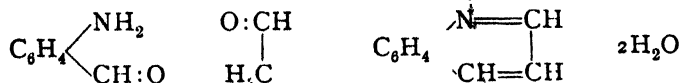
There are three main stages in the Skraup synthesis: (a) the condensation of a primary aromatic amine with an unsaturated aldehyde (usually acrolein); (b) ring-closure of the product to give a 1:2-dihydroquinoline; and (c) oxidation of the latter to the quinoline.

(2) Fundamentally similar to the Skraup synthesis is that of *Döbner* and *von Miller*, the chief difference being the method used to dehydrogenate the intermediate 1:2-dihydroquinoline.



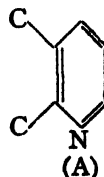
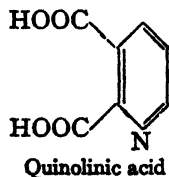
An aromatic primary amine, an aldehyde and concentrated hydrochloric acid are mixed together and heated. The reaction with aniline and acetaldehyde (paraldehyde) is represented as follows. Acetaldehyde condenses to aldol, which is dehydrated to crotonaldehyde. The latter combines with aniline forming dihydroquinaldine (compare Skraup mechanism) and this is then dehydrogenated to quinaldine by Schiff's bases formed during the reaction such as ethylideneaniline, $\text{CH}_3\text{CH}:\text{NPh}$, which are reduced to ethylaniline, etc. The Döbner-von Miller synthesis thus yields homologues of quinoline, and by employing other aldehydes of the formula $\text{R.CH}_2\text{CHO}$ in place of acetaldehyde and other amines instead of aniline, it is possible to prepare a great number of quinoline derivatives.

3. Another synthesis of general application is that discovered by Friedländer, who obtained quinoline by condensing *o*-amino-benzaldehyde with acetaldehyde. *o*-Aminobenzaldehyde is inconveniently sensitive and *o*-aminobenzylidene arylamines may be used with advantage instead.¹

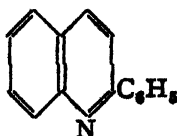


Once again, the *o*-amino-benzaldehyde may be replaced by its substitution products, by *o*-amino-phenyl ketones or *o*-amino-benzoic acid, and in place of acetaldehyde other compounds containing the group CH_2CO may be used, *i.e.* aldehydes, ketones, acetoacetic ester and malonic ester. These reactions proceed very readily in dilute aqueous solutions if the pH value is carefully controlled.²

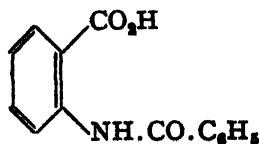
Structure.—The structure of quinoline has been clearly established by the syntheses of Friedländer and Baeyer and has been confirmed by



the chemical behaviour of quinoline and its derivatives. When quinoline is oxidised by means of alkaline potassium permanganate, or better, with hydrogen peroxide³ it yields quinolinic acid, thereby establishing the presence of a pyridine fragment (A) in the molecule. The presence of a benzene nucleus is proved by the oxidation of 2-alkyl- or aryl-quinolines



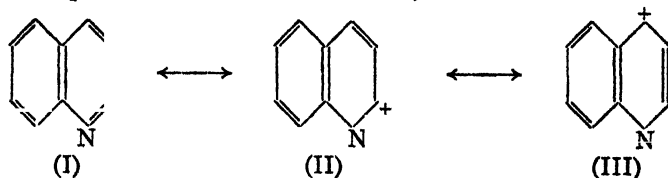
[O]



¹ A. Rilliet and L. Kreitmann, *Helv. Chim. Acta*, 1921, 4, 596; 1922, 5, 547. ² C. Schöpf and G. Lehmann, *Ann.*, 1932, 497. ³ W. Stix and S. A. Bulgatsch, *Ber.*, 1932, 65, 11.

with potassium permanganate when N-alkyl or aryl-anthranilic acids are obtained. 2-Phenylquinoline, for example, yields benzoyl-anthranilic acid.

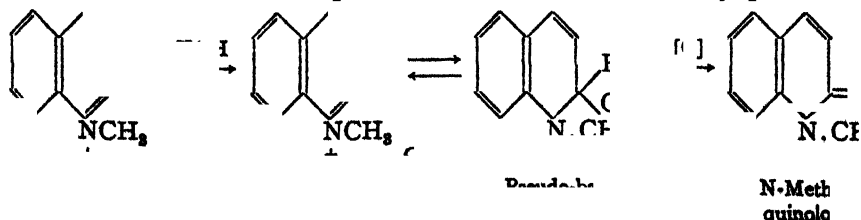
The structure assigned is very similar to that of naphthalene, the only difference being the replacement of a methine group (CH) in the naphthalene molecule by a nitrogen atom in the quinoline. This resemblance is emphasised by the similarity of the absorption spectra of the two compounds and of their resonance energies (77 and 75 Kcal./mole for naphthalene and quinoline respectively). Contributing to the resonance of quinoline are forms such as I, II and III.



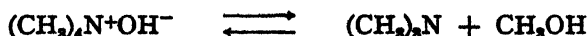
Properties.—In chemical behaviour quinoline resembles pyridine and forms salts, reacts with methyl iodide to form the quaternary salt, N-methylquinolinium iodide, and is oxidised by perbenzoic acid to the N-oxide. As would be expected from the greater ease of reduction of pyridine in comparison to that of benzene, reduction of quinoline (by zinc and hydrochloric acid or sodium and ethyl alcohol) attacks the pyridine ring giving 1:2:3:4-tetrahydroquinoline. It is also to be anticipated that electrophilic substitution will occur much more readily in the benzene ring than in the pyridine ring. Nitration does in fact give 5- and 8-nitroquinoline which on further nitration yield 5:7- and 6:8-dinitroquinoline respectively. Controlled bromination, however, gives 3-bromoquinoline.

As in the pyridine series substituents in the 2- and 4-position of the quinoline molecule are frequently very reactive. 2- and 4-Halogenoquinolines when attacked by alkaline reagents readily lose the halogen atoms in exchange for basic radicals. 4-Chloroquinoline, for instance, readily gives 4-aminoquinoline when heated in phenol with ammonia. This is an example of nucleophilic attack and its occurrence at the 2- and 4-positions is readily accounted for by the resonating forms II and III (above). 2- and 4-Methylquinolines behave towards aldehydes in the same manner as the corresponding methylpyridines (p. 716 *et seq.*).

If a quinolinium salt is treated with alkali, ammonium base—carbinol isomerisation occurs and a *pseudo-base* is formed. N-Methylquinolinium



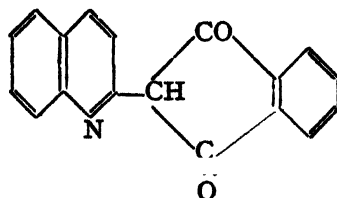
iodide, for example, with alkali gives the corresponding quaternary hydroxide which is equilibrium with the pseudo-base or carbinol base, the structure of which follows from its oxidation with potassium ferricyanide to N-Methylquinolone. In contrast to the ammonium base, the pseudo-base is soluble in benzene and its aqueous solution is non-conducting. The formation of the pseudo-base is comparable to that of the dissociation of a quaternary ammonium hydroxide into a tertiary base and an alcohol



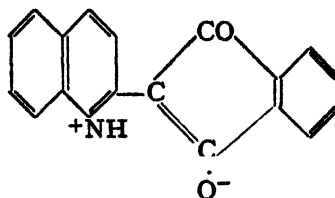
Homologues of Quinoline

All the seven theoretically possible methylquinolines are known. The four containing the methyl group in the benzene nucleus are generally termed *toluquinolines*.

Quinaldine, *2-methylquinoline*, b.p. 247° , is found with quinoline in coal-tar. Its preparation and reactivity have already been discussed. The reactivity of the methyl group is shown by the formation of the dye, **Quinoline Yellow**, from quinaldine and phthalic anhydride. The older formulation of Quinoline Yellow has been replaced by an *enol-betaine structure* which accounts more satisfactorily for the properties of the compound.



Older Formula



Enol-betaine formula

Quinoline Yellow

Lepidine, *4-methyl-quinoline*, b.p. 257° , is also present in coal tar.

Cyanine Dyes¹

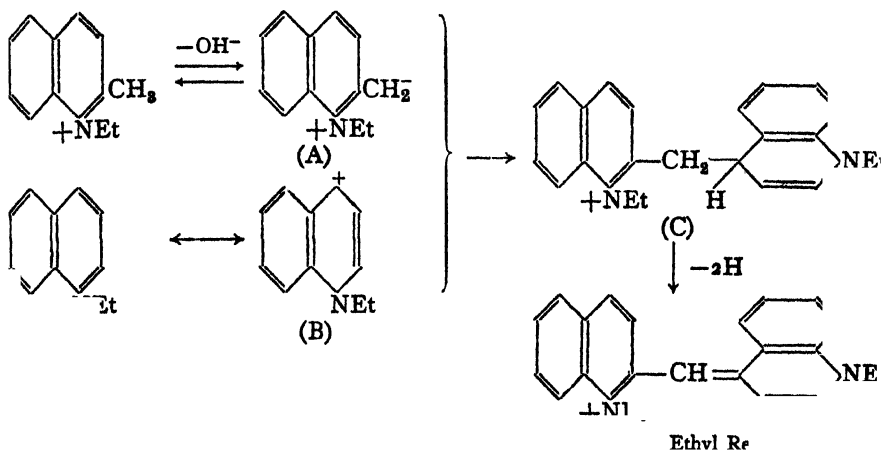
Two quinoline dye-stuffs have already been discussed: Alizarin Blue (p. 600) and Quinoline Yellow. The most important quinoline dye-stuffs, however, are the **Cyanine Dyes**, in which two quinoline nuclei are separated by a methine ($\cdot\text{CH}:$) group or a trimethine group ($:\text{CH}.\text{CH}:\text{CH}\cdot$). As will be seen from the examples discussed below the cyanine dyes contain conjugated systems separating two nitrogen atoms, one of which is tertiary and the other quaternary.

Although too fugitive for use in dyeing fabrics the cyanine dyes are of the utmost importance for rendering photographic plates more sensitive to light of any desired part of the spectrum.

¹ F. M. Hamer, *The Cyanine Dyes*, *Quart. Reviews*, 1950, 4, 327.

The cyanine dyes may be divided into three main groups depending on the heterocyclic nuclei employed and the carbon chain binding these nuclei.

(I) **Monomethine Cyanines.** As the name implies these dyes contain two heterocyclic nuclei separated by a methine group. A typical example of this type is **Ethyl Red** whose formation and constitution may be used to illustrate the essential features of the cyanine dyes. The ethiodides of quinoline and quinaldine are condensed in the presence of alkali and the product is oxidised to the dye-stuff. The reaction may be represented by the following chart in which the 2-methylquinolinium cation under the influence of the alkali loses a proton to give the polar form A, which with the quinolinium cation (B) gives the product C. In other words the quinolinium ion (B) undergoes nucleophilic attack by A. The product

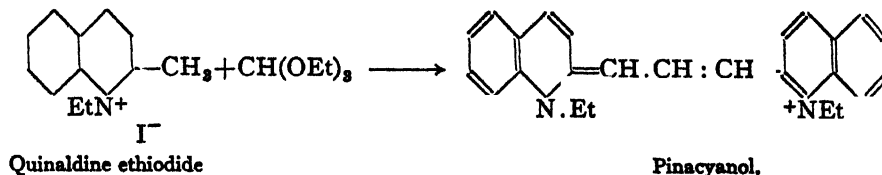


C is immediately oxidised by other constituents of the reaction mixture to give Ethyl Red. Such a dye-stuff is undoubtedly a resonance hybrid similar to that shown in the carbocyanines (see below).

Ethyl Red is representative of the class of dye-stuff in which the heterocyclic nuclei are joined through a 2 : 4'-linkage (plain numbers refer to the quinaldine and numbers with a dash to the quinoline nucleus) and are termed **isocyanines**. Another member of this series is **Pinaverdol** or **Sensitol Green** which is prepared by heating a mixture of quinoline methiodide and 2 : 6-dimethylquinoline methiodide with alcoholic sodium hydroxide. These dyes sensitise photographic plates as far as the orange region.

The isomeric compounds with a 4 : 4'-linking are known as **cyanines** and are of little value. They may be prepared by treating a mixture of quinoline and 4-methylquinoline methiodides with alcoholic potassium hydroxide. The corresponding 2 : 2'-derivatives (ψ -cyanines) were first obtained by heating a mixture of 2-iodoquinoline methiodide and quinaldine methiodide with alcoholic potassium hydroxide.

(2) **Trimethine Cyanines or Carbocyanines.**—These contain the quinoline nuclei joined through a $:CH.CH:CH.$ chain, and have been shown by Miss Hamer to be best obtained when a quinaldine alkiodide is heated in pyridine with an excess of ethyl ortho-formate.



Carbocyanines, of which **Pinacyanol** or **Sensitol Red** is one of the most important, sensitise photographic plates in the yellow and red regions. Various other types of carbocyanines may also be prepared by Hamer's method. For example, **kryptocyanine** (1 : 1'-diethyl-4 : 4'-carbocyanine iodide), is obtained by using 4-methyl-quinoline (lepidine) ethiodide. This sensitises strongly in the red and infra-red, although not in the green.

As already stated, the cyanine dyes contain resonating systems. Thus the carbocyanines contain resonating molecules represented by I and II.



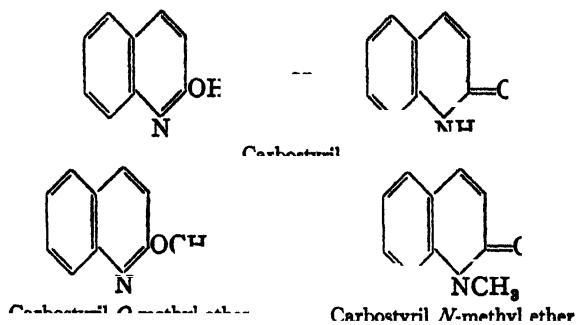
(3) **Cyanines containing Heterocyclic Rings other than Quinoline.**—A description of these compounds is given in Miss Hamer's article referred to on p. 728.

Hydroxy-quinolines

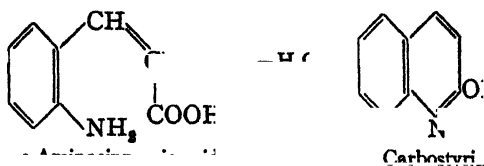
The hydroxy derivatives of quinoline possess the basic character of quinoline as well as the acidic character of phenol.

Hydroxy-quinolines containing the hydroxyl group in the 2- or 4-position of the pyridine nucleus exhibit the same tautomerism as the hydroxy-pyridines (see p. 717). They react in the hydroxylic form as true hydroxy quinolines, and also in the ketonic forms as quinolones. For example, the silver salt of carbostyryl gives the O-ether, while the sodium salt gives both the O- and N-ethers. Phosphorus pentachloride converts carbostyryl to 2-chloroquinoline, thus showing the presence of a hydroxyl group, but ferric chloride gives no coloration. The classic researches of Hartley and Dobbie showed that in ethanol carbostyryl is essentially ketonic, since the ultra-violet spectrum of the solution resembles that of the N-ether and differs from that of the O-ether.

The 3-, 5-, 6-, 7-, and 8-hydroxyquinolines on the other hand cannot undergo tautomerism and therefore behave as phenolic compounds.



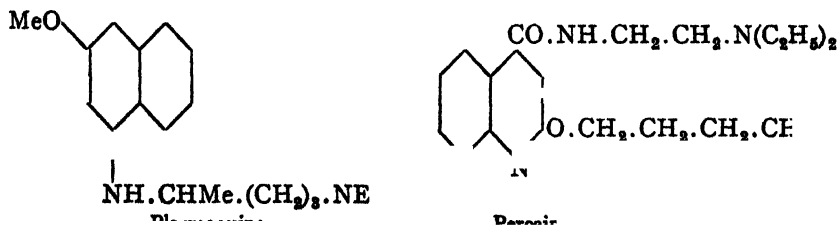
Carbostryl, 2-hydroxyquinoline, m.p. (anhydrous) 201° , is obtained by the reduction of *o*-nitrocinnamic acid with ammonium sulphide. Hence it is to be regarded as an inner anhydride (lactam or lactim) of



Kynurine, 4-hydroxyquinoline, m.p. 201° , is formed by heating kynurenic acid (see p. 674) or by the oxidation of cinchonine.

Oxine, 8-hydroxyquinoline, is widely used in qualitative inorganic analysis for the detection of metals such as magnesium, aluminium, etc.

Plasmoquine, a derivative of 6-methoxyquinoline, was formerly employed as a specific against malaria.



Like quinine it is a derivative of 6-methoxyquinoline. Percaïne is a local anaesthetic about ten times as powerful as cocaine.

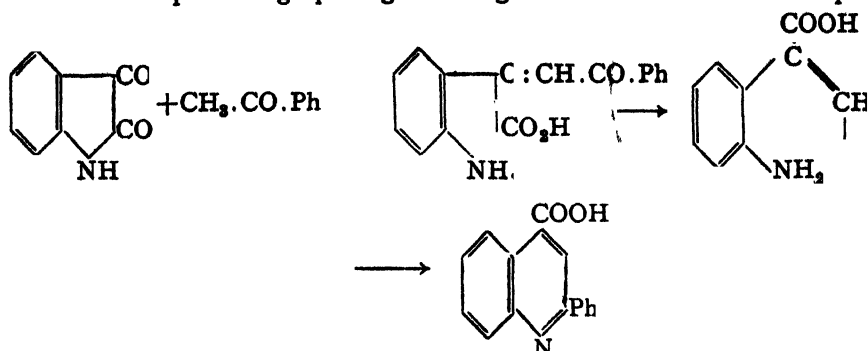
Quinoline Carboxylic Acids

All of the carboxylic acids corresponding to the seven methylquinolines are known. Those containing the carboxyl group in the benzene ring may be prepared from amino-benzoic acids by Skraup's synthesis.

Among quinoline carboxylic acids containing the carboxyl group in the pyridine ring, the following may be mentioned :

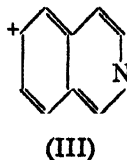
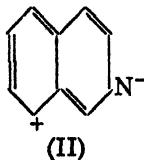
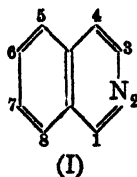
Quinaldinic acid, *quinoline-2-carboxylic acid*, results from the oxidation of quinaldine with chromic acid. It is also conveniently prepared in good yield by heating quinaldine with formaldehyde and oxidising the methylol-compound so obtained with nitric acid. Its structure follows from these syntheses and from its conversion into quinoline on decarboxylation.

Atophane, *2-phenyl-quinoline-4-carboxylic acid*, is used as a remedy in arthritic diseases owing to its power of removing uric acid from the system. It is obtained by the *Pfitzinger reaction* in which isatin is made to condense with ketones (in this case acetophenone) or acids in presence of alkali, with subsequent ring-opening and ring-closure as shown in the equation.



ISOQUINOLINE¹

In isoquinoline as in quinoline a pyridine ring is fused with a benzene ring, but the union is not in the 2 : 3- but in the 3 : 4-position of the pyridine nucleus. Isoquinoline may therefore be considered as naphthalene



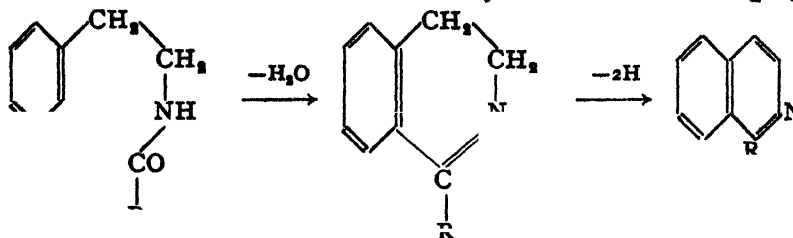
in which one of the CH-groups in the β -position has been replaced by a nitrogen atom. Like naphthalene and quinoline, isoquinoline is a resonating compound with the main contributing forms structures such as I. Minor contributions come from forms II and III.

Isoquinoline occurs in coal-tar and is obtained commercially from this source. Many alkaloids contain an isoquinoline ring, particularly the 1-benzylisoquinoline ring (p. 774).

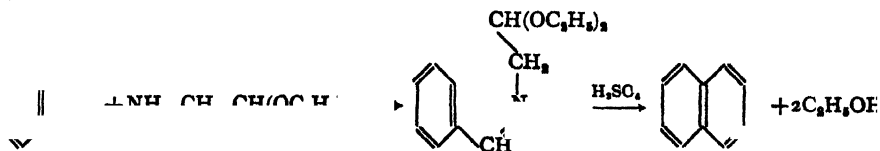
Among syntheses proving the structure of isoquinoline and its derivatives, the following may be mentioned.

¹ *The Chemistry of Isoquinoline*, R. H. Maske, *Chem. Rev.*, 1942, 30, 145. *Isoquinoline*, by W. J. Genies, in *Heterocyclic Compounds* (Editor, R. C. Elderfield, 4, 344.)

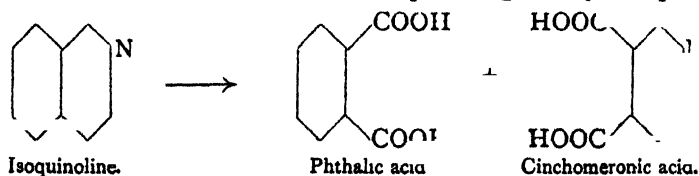
(1) One of the most important methods of preparing isoquinoline compounds is by the dehydration of acyl derivatives of phenylethylamine with agents such as phosphorus pentoxide in boiling xylene (*Bischler-Napieralski* method¹). The dihydro-compound is dehydrogenated by palladium, a reagent much used for this purpose. An example of the application of this method is found in the synthesis of cotarnine (p. 779).



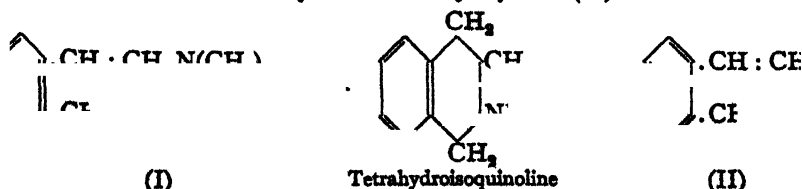
(2) In the *Pomeranz-Fritsch* synthesis² no dehydrogenation is required. A benzaldehyde is condensed with an amino-acetal to give a benzylideneamino-acetal, which on treatment with sulphuric acid undergoes ring-closure and forms an isoquinoline.



The constitution of isoquinoline has been confirmed by the oxidative degradation of isoquinoline and its derivatives. Oxidation of isoquinoline with alkaline potassium permanganate attacks both the benzene ring and the pyridine ring, and a mixture of phthalic acid and cinchomeronic acid is obtained. Oxidation with neutral permanganate yields phthalimide

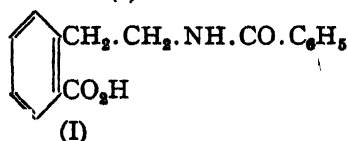


The degradations of 1:2:3:4-tetrahydroisoquinoline are also in harmony with the accepted structure of isoquinoline. Hofmann's exhaustive methylation method gives the unsaturated tertiary amine (I), whereas the Emde method yields *o*-methylstyrene (II).



¹ For a review of the reaction see W. M. Whaley and T. R. Govindachari in *Organic Reactions* (Editor, Roger Adams), vol. VI, p. 74. ² For a review of the reaction, see W. Genieser, *Organic Reactions* (Editor, Roger Adams), vol. VI, p. 101.

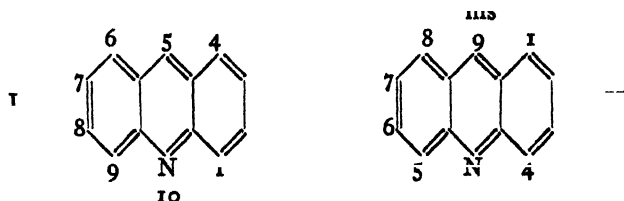
Isoquinoline, m.p. 23° and b.p. 240° , is found in small amount with quinoline in coal-tar, and can be separated from the latter by taking advantage of the low solubility of its sulphate. It is a colourless liquid which resembles quinoline in many respects. It is a typical tertiary amine, pK_a 4.95, yielding the N-oxide on oxidation with perbenzoic acid and forming quaternary ammonium salts with alkyl halides. It is to be expected that electrophilic substitution will occur in the benzene ring and nucleophilic substitution in the pyridine ring, especially in position-1. These expectations have on the whole been realised. Nitration occurs mainly at the 5-position (possibly also to a much smaller extent at the 8-position). Sodamide, on the other hand, affords 1-aminoisoquinoline. Bromination, however, yields 4-bromoisoquinoline. As would be anticipated from the comparative ease with which pyridine is hydrogenated, the reduction of isoquinoline gives 1:2:3:4-tetrahydroisoquinoline, whose structure has been established by synthesis from β -phenylethylamine, and by the oxidative degradation of the N-benzoyl compound to the benzoylated amino-acid (I).



Acridine Group

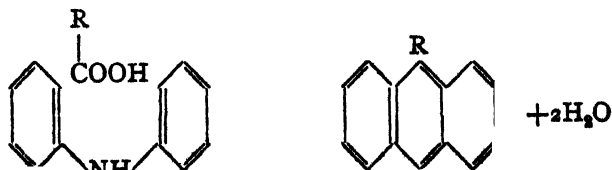
Acridine is a dibenzo-pyridine, and stands to quinoline in the same relationship as anthracene to naphthalene. It may be regarded as anthracene in which one of the central CH-groups is replaced by N.

The numbering of the nucleus now generally adopted in British publications is given in I; that shown in II is usually found in German and American journals. The former numbering is used in this text.



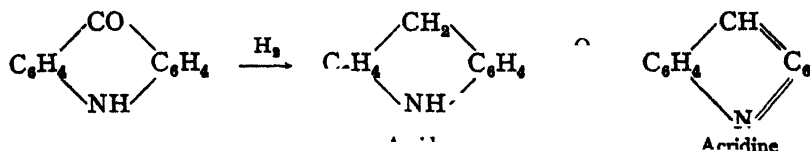
The acridines may be synthesised by a number of methods some of which establish their structure.

(1) In the first synthesis of acridine derivatives (Bernthsen) diphenylamine and carboxylic acids are heated together in the presence of a

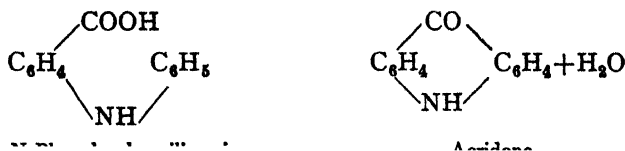


dehydrating agent (zinc chloride). Good yields are often obtained, but with formic acid acridine is obtained in only 7.5 per cent. yield.

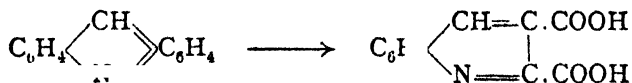
(2) Reduction of the acridones (see below) gives acridines. Acridone, for example, is reduced by sodium and amyl alcohol to *acridane*, which on oxidation with potassium dichromate and sulphuric acid affords a good yield of acridine.



Acridone is prepared by the ring-closure of diphenylamine-2-carboxylic acid (N-phenylanthranilic acid) by means of sulphuric acid.



The structure of acridone and consequently of acridine follows from this synthesis and is confirmed by the oxidation of acridine to *acridini acid* (quinoline-2 : 3-dicarboxylic acid).

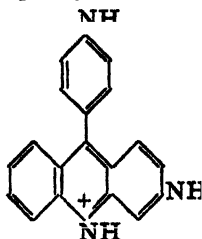


Acridine was discovered by Graebe and Caro (1870) in the crude anthracene of coal-tar and is the parent substance of various dye-stuffs of industrial value. It crystallises in colourless needles, m.p. 110°, and in solution has a blue fluorescence, a property peculiar to all the acridine bases. This fluorescence is particularly pronounced in ethereal solution. Acridine is a weak base, pK_a 5.60, comparable to aniline. It is very similar to anthracene and like this hydrocarbon is very stable. It is not attacked even when fused with potassium hydroxide. Acridine has a resonance energy of 106 Kcal./mole (*cf.* anthracene 105 Kcal./mole); has a perfectly planar molecule; and its absorption spectrum is almost identical with that of anthracene. It resembles anthracene too in undergoing reduction at the *meso*-positions to give 5 : 10-dihydroacridine (acridane), but on oxidation it yields only a small quantity of acridone. Certain substituted acridines, on the other hand, are converted by this method into the corresponding acridones in excellent yield.

Nitration of acridine yields the four mononitro-acridines, the main product being 3-nitro-acridine. 1-Nitro-acridine to a smaller extent and traces of the 2- and 4-isomers are obtained.

By the entrance of amino-groups (auxochromes) into the acridine molecule it acquires the properties of a dye, the pyridine ring functioning as the chromophore group. The resulting dye-stuffs generally contain the amino-groups in positions 2 and 8.

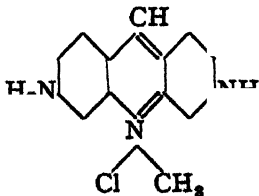
Chrysaniline, 5-*p*-aminophenyl-2-amino-acridine,



is the oldest acridine dye-stuff. It was first observed by W. H. Perkin Sen., as a by-product in the manufacture of magenta and was later isolated by Nicholson as the sparingly soluble nitrate. Its constitution was established by O. Fischer and Körner, by synthetic and analytical methods. For example, on diazotisation and boiling with alcohol it gives *m*s-phenylacridine. It may be synthesised by the condensation of *o*-nitrobenzaldehyde with aniline to form *o*-nitro-*p*-diamino-triphenyl methane; the latter can then be reduced to the triamino-compound which yields chrysaniline on oxidation. The crude nitrate or hydrochloride is placed on the market under the name of "**Phosphine**." It dyes wool and silk directly and cotton with the aid of tannin mordant, giving an orange-tinted yellow colour. It is chiefly used for silk.

Among the acridine compounds which are utilised as antiseptics the following 2 : 8-diaminoacridine derivatives may be mentioned. Pure 2 : 8-diaminoacridine is obtained in 70 per cent. yield by heating *m*-phenylene-diamine with oxalic or formic acid and is now manufactured in this way.

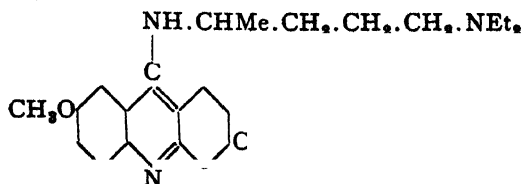
Proflavine ($C_{18}H_{13}N_3$)₂, H_2SO_4 , $2H_2O$, the neutral sulphate is a red hygroscopic powder and is used for wounds and gonorrhœa. The methochloride of 2 : 8-diaminoacridine is a valuable antiseptic and its hydrochloride with approximately one-third of its weight of 2 : 8-diaminoacridine hydrochloride constitutes the drug **acriflavine**.



2 : 8-Diamino-10-methylacridinium hydrochloride

It may be mentioned that there is considerable confusion in the literature as to the meaning of the term acriflavine. It is used above as defined in the *British Pharmacopœia*.

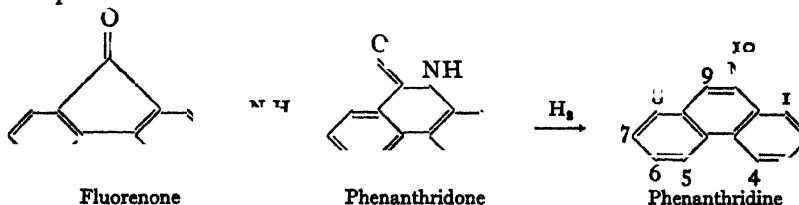
5 : 8-Diamino-acridine and its substitution products are also therapeutically effective against streptococci. The highest activity in this sense is shown by **rivanol**, the hydrochloride of 3-ethoxy-5 : 8-diamino-acridine. **Atebrin** or **mepacrine**, which was formerly employed in the treatment of malaria, has been formulated as follows :



It has been largely superseded by paludrine (p. 867).

Phenanthridine

Isomeric with acridine is **phenanthridine**, 3 : 4-benzoquinoline. It occurs in coal-tar and can be synthesised by a number of methods. It is prepared from its oxygenated derivative **phenanthridone**, which is conveniently obtained by the action of hydrazoic acid on fluorenone, an imino group being thus inserted between the carbonyl group and a benzene ring. Fluorenone is also converted into phenanthridone by the action of phosphorus pentachloride on the oxime (Beckmann transformation). Reduction of phenanthridone by lithium aluminium hydride yields phenanthridine.



Derivatives of the quaternary salts of phenanthridine, the *phenanthridinium salts*, are useful trypanocides and to a lesser extent antiseptics. **Dimidium Bromide**, for example, is 2 : 7-diamino-9-phenyl-10-methylphenanthridinium bromide and has been used in the treatment of diseased African cattle.

VII

The Vegetable Alkaloids¹

Introduction

The alkaloids are now generally defined as basic compounds of vegetable origin, in which at least one nitrogen atom forms part of a cyclic system. This definition, however, does not include certain members of the group. Many of these compounds possess curative properties and are of great value in medicine.

¹ See T. A. Henry, *The Plant Alkaloids* (Churchill). Lyndon Small in *Gilman's Organic Chemistry*, 2, 1018.

Although the poisonous and therapeutic properties of various plants have been known and utilised from early times, it was not until 1817 that the first alkaloid was isolated. A large number of these compounds are now known, but for a long time all attempts to determine their constitutions or to prepare them synthetically were fruitless.

The chemistry of the alkaloids began to make definite progress with the discovery of pyridine and quinoline, which led to the view that they were related to these bases in the same manner as aromatic compounds to benzene. Königs, in 1880, defined alkaloids as naturally occurring organic bases which are derived from pyridine.

This suggestion proved of great value in promoting our knowledge of the chemistry of pyridine, but did not hold true for all alkaloids. Later, the systematic classification of the alkaloids as derivatives of pyridine, or indeed as belonging to any single class of organic compound, had to be abandoned, owing to the discovery that natural groups of vegetable bases, such as the morphine and coca groups, cannot be referred to any one parent substance but belong to a number of different systems.

In describing all the vegetable bases as alkaloids, we are therefore collecting into one class a number of substances of widely differing constitutions. A few of these contain nitrogen in an open chain, but in general it is present in a cyclic structure such as that of pyridine, quinoline, isoquinoline or pyrrole. Still other alkaloids are derived from purine, or from complex dicyclic systems such as are contained in the "second half" of the cinchona alkaloids and in the tropine group.

Preparation of Alkaloids from Plants and their general Properties.

Alkaloids are usually found in plants in the form of salts—in which they are either united to the common plant acids (*e.g.* malic or citric acid) or to certain characteristic acids such as quinic acid, in the cinchona alkaloids, and meconic acid, in those of the opium group. Their distribution is very unequal. Although they may be detected in all parts of the plant, they generally accumulate in the fruit and seeds, and also in the bark of trees.

In the preparation of alkaloids from plants the finely divided material is usually extracted with water containing hydrochloric or sulphuric acid. This liberates the alkaloids from their salts with organic acids, and the bases pass into solution as hydrochlorides or sulphates, together with dye-stuffs, carbohydrates and other products from the plant tissue. From the solution so obtained the alkaloids, being insoluble or only sparingly soluble in water, can be precipitated by the addition of alkali. If the bases are volatile, as in the case of nicotine, the solution or finely divided raw material is treated with alkali and distilled in steam. The crude alkaloids are then purified by special methods, frequently by recrystallisation of the free compounds or their salts.

The majority of the alkaloids are solid substances which cannot be distilled; only a few, such as coniine, are liquid and volatilise without

decomposition. On the animal organism, as has already been mentioned, they often exert a marked physiological action. Almost without exception they are either insoluble or sparingly soluble in water, dissolve with more or less difficulty in chloroform, ether and benzene, and readily in alcohol. Most of the alkaloids are optically active and usually laevorotatory. In many cases their solutions give a strong alkaline reaction.

All of them form salts with acids, among which the hydrochlorides, sulphates and oxalates crystallise particularly well. Like the salts of other bases, they possess the property of uniting with certain metallic salts such as the chlorides of mercury, platinum and gold, to form double compounds.

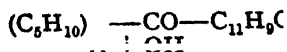
Alkaloids are precipitated from aqueous or acid solution by a number of substances generally known as *alkaloid reagents*, e.g. tannic acid, picric acid, picrolonic acid, perchloric acid, potassium mercuric iodide, potassium bismuth iodide, phosphomolybdic acid and phosphotungstic acid. These reagents, however, are of no great value for the quantitative analysis of alkaloids, since the resulting compounds are not sufficiently insoluble and because the reagents also precipitate other organic substances.

Methods of Determining the Chemical Constitution of the Alkaloids

In attempting to determine the structure of an alkaloid many methods are available of which the following are representative.

1. The alkaloid is isolated in a pure state, its *molecular weight* and *empirical formula* then determined, and its optical *rotatory power* measured.

2. Frequently an alkaloid may be broken into simpler fragments by *hydrolysis* with water, alkali, or acid, and the fragments examined separately, the structural determination of such fragments being patently easier than that of the whole molecule. Thus piperine decomposes on hydrolysis into piperidine and piperic acid; hence the union is of the acid amide type.

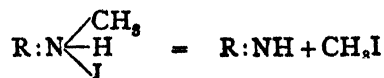


Atropine, as will be seen later, may be hydrolysed to give tropic acid and the alcohol tropine.

Hydrolytic fission is sometimes accompanied by other changes, since the resulting basic portion may be attacked or undergo racemisation. Care must accordingly be exercised in interpreting the results of hydrolysis.

3. *Function of the nitrogen atom or atoms.*—In most alkaloids the nitrogen is in a ring structure and must be secondary or tertiary. It is frequently difficult to distinguish between these possibilities, but the nitrogen is assumed to be tertiary if the secondary amino group tests (e.g. benzoylation) are negative. *Methylimino-groups*, present in many

alkaloids, are quantitatively estimated by the method of Herzig and Meyer, in which the alkaloid hydroiodides are heated to 200-300° and the resulting methyl iodide estimated by absorption in an alcoholic silver nitrate solution and the resulting silver iodide weighed.

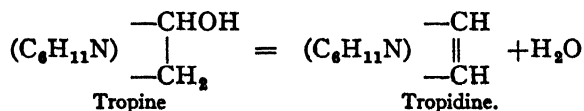


Further information regarding the nature and position of nitrogen atoms is gained by exhaustive methylation (see below).

4. *Function of the oxygen atom or atoms.*—Standard methods, used to evaluate the function of the oxygen, are summarised below.

(a) *Phenolic.*—Solubility in sodium hydroxide ; colours with ferric chloride ; benzoylation, etc.

(b) *Alcoholic.*—Reaction with phosphorus pentachloride or thionyl chloride. Sometimes an alkaloid containing an alcoholic hydroxyl group is converted into its anhydro-compound by means of dehydrating agents such as a solution of sulphuric acid in glacial acetic acid (*e.g.* tropine → tropidine).



The unsaturated compounds so obtained are often more reactive than the original alkaloids, and can with advantage be submitted to reactions involving further degradations.

(c) *Carboxyl.*—Solubility in sodium carbonate solution ; esterification, etc.

(d) *Methoxyl.*—Zeisel's method is used for the determination of methoxyl groups and depends on the conversion of the methyl of the CH₃O-group into methyl iodide by boiling with hydriodic acid and estimating the methyl iodide as described above.

A process for the *determination of methoxyl in the presence of methyl-imino groups* (Herzig and Meyer) is based on the fact that the methoxyl group is hydrolysed at the boiling-point of hydriodic acid, whilst the N-methyl group is not detached until a higher temperature has been reached.

(e) The *methylenedioxy*-group, $\text{CH}_2 \begin{array}{l} \swarrow \text{O} \\ \searrow \text{O} \end{array}$, is identified and estimated

quantitatively by means of sulphuric acid which splits off formaldehyde.

(f) The presence of *carbonyl*-groups is shown by the standard reagents such as phenylhydrazine, semicarbazide, etc.

(g) *Lactones* are usually detected by hydrolysis to the parent hydroxy-acids.

5. *Oxidation* frequently gives valuable information about the fundamental structure of alkaloids and the position of nitrogen and oxygen atoms or functional groups such as the methoxy. For example, the oxidation of coniine to picolinic acid (pyridine-2-carboxylic acid) shows it to be an α -substituted pyridine derivative. Among the oxidising reagents used the most important are potassium permanganate, chromic acid, nitric acid, and hydrogen peroxide. Permanganate is of particular value in attacking a double bond between carbon atoms, when two hydroxyl groups are first added (see p. 124). The resulting glycols are best further oxidised by means of chromic acid, which leads to the molecule being ruptured at the point originally occupied by the double bond.

Many examples of the value of oxidation in alkaloid chemistry will be found in the following pages.

6. In the *hydrogenation of alkaloids* an important part is played by *catalytic methods of reduction*, involving the use of metals of the platinum group. In this manner morphine readily yields dihydro-morphine, and the cinchona alkaloids give dihydro-derivatives.

7. Vigorous reactions such as degradation by *distillation with zinc dust, alkali fusion, heating with bromine*, etc., often result in the isolation of some stable parent compound. Gerhardt, as early as 1842, obtained quinoline from cinchonine by distilling the latter with alkali. Vongerichten and Schrötter isolated phenanthrene as the main product of the distillation of morphine with zinc dust. Alkaloids containing oxygen generally lose this element on treatment with zinc dust, while those rich in hydrogen become dehydrogenated. Our knowledge of the constitution of coniine, for example, is based on Hofmann's observation that on distilling the compound with zinc dust it loses six hydrogen atoms to give conyryne (2-propyl-pyridine).

8. *Ring-fission*.—An interesting method frequently employed in examining the structure of alkaloids is to study the degradation products they yield on *exhaustive methylation*, by which in its widest sense is understood the decomposition of substituted ammonium hydroxides under the influence of heat, or of quaternary ammonium salts when treated with alkalis. The reactions employed in the exhaustive methylation of alkaloids are well illustrated by the degradation of N-methyl-piperidine to piperylene (see p. 722), a classical example discovered by A. W. Hofmann. Other simple examples will be found under hordenine, coniine, and aporphine. In this manner the carbon framework of the alkaloid molecule is revealed in the form of unsaturated hydrocarbons.

This method of decomposition may be applied to alkaloids with all conceivable groupings in the molecule, and also, which is of special importance, to amino-acids obtained by the oxidation of alkaloids. The degradation products formed in this way include a great variety of unsaturated non-nitrogenous compounds, including hydrocarbons, ketones, aldehydes and carboxylic acids. For determining the structure of alkaloids

this method is therefore of great service, since these unsaturated products of exhaustive methylation can often be converted by simple reactions, such as reduction, into compounds of known constitution.

Tropinic acid, for example, on exhaustive methylation gave a diolefin-dicarboxylic acid of the formula $C_7H_8O_4$, and of unknown structure; on reduction with sodium amalgam this was transformed into pimelic acid, a normal dicarboxylic acid containing seven carbon atoms (see p. 288).

Hence it follows that the carbon skeleton in tropine and ecgonine must possess an unbranched chain of seven atoms, and that these are arranged in the form of a ring, since tropinic acid is produced from tropine and ecgonine by rupture of part of the cyclic system. The application of the same principle also enabled this cycloheptane ring to be isolated intact from cocaine and atropine, in the form of its ketone, suberone.

The value of exhaustive methylation, followed by reduction of the resulting degradation products, is not confined to the information this gives concerning structure, as it is often possible to effect a synthesis of the alkaloid by applying the method in the reverse direction.

The *fission of cyclic bases by means of phosphorus halides* (J. v. Braun) has also been applied to the determination of alkaloid structure. This treatment yields open-chain halogen compounds (see p. 721).

Classification of the Alkaloids.—In the succeeding pages the alkaloids are classified according to their chemical constitution, especially with reference to the basic compounds from which they are derived. In most cases it is then found that alkaloids produced by one and the same plant, and therefore belonging to the same botanical group, also fall into the same chemical group, owing to the fact that the compounds generated by a given plant frequently possess similar chemical constitutions.

The alkaloids are therefore divided into the following groups :

1. Hydroxy-phenyl alkylamine and phenyl hydroxy-alkylamine bases.
2. Alkaloids of the pyridine group.
3. Alkaloids of the pyrrolidine group.
4. Alkaloids of the indole group.
5. Alkaloids of the quinoline group.
6. Alkaloids of the isoquinoline group.
7. Alkaloids of the phenanthrene group.

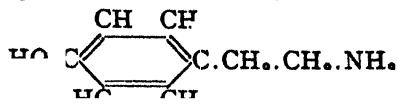
Like every classification this is somewhat arbitrary. It may be objected that the alkaloids atropine and cocaine, treated under the pyrrolidine group, also contain a pyridine nucleus, and should therefore have been included in the pyridine group. It seemed, however, more convenient to treat these compounds in a group by themselves. The seventh group is termed the phenanthrene group, and under this head will be found morphine, codeine and thebaine.

I.—HYDROXY-PHENYL ALKYLAMINE AND PHENYL HYDROXY-ALKYLAMINE BASES

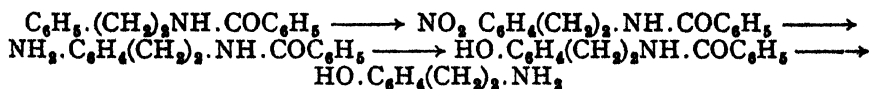
Organic bases possessing phenolic character have valuable pharmacological properties. Adrenaline (p. 858) is an important drug; hordenine, present in fermenting barley, has striking properties (Leger); and Barger identified in *p*-hydroxyphenyl-ethylamine one of the constituents of ergot (in diseased rye seed) which gives rise to its characteristic activity.

In addition to these compounds, thyroxine, which is described in the section on hormones, has been synthesised by Barger and Harington.

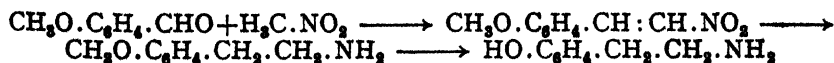
p-Hydroxyphenyl-ethylamine



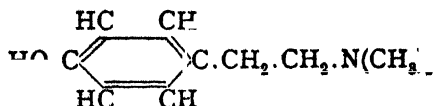
This compound was shown by Barger¹ to be present to the extent of 0.1 to 1 per cent. in ergot, in which it is accompanied by 4-β-aminoethyl-glyoxaline (β-iminazyl-ethylamine). Physiologically, it has the effect of strongly increasing the blood pressure. It may be isolated from the aqueous extract of ergot by shaking out with amyl alcohol, and crystallises in white needles or leaflets, m.p. 160°, b.p. 161° to 163°/2 mm. pressure. *p*-Hydroxyphenyl-ethylamine may be synthesised by various methods, *e.g.* benzyl cyanide on reduction yields phenyl-ethylamine, the benzoyl derivative of which is converted into the hydroxy-phenyl compound by nitration, followed by reduction and diazotisation. On removing the protective benzoyl group by hydrolysis, *p*-hydroxyphenyl-ethylamine is obtained.



A better yield is obtained by condensing anisaldehyde with nitromethane to form *p*-methoxy-nitrostyrole, which is then reduced and the methyl group removed with hydriodic acid.



Hordenine, *p*-Hydroxyphenyl-dimethylethylamine

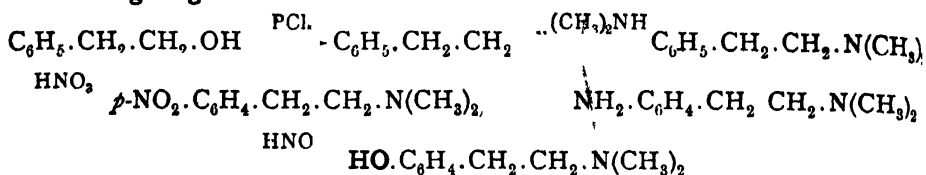


Hordenine is present in the embryo of barley and in various cacti. The researches which led to its discovery were prompted by the use made of germinating barley in southern France and some of the French colonies

¹ G. Barger, *J.*, 1909, 95, 1123. An even more active principle, *ergometrine*, was later isolated from ergot by H. W. Dudley (*Proc. Roy. Soc.*, 1935, B, 128, 478).

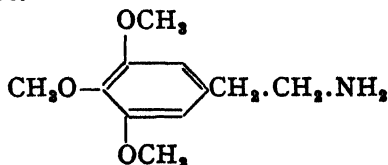
as a remedy for diarrhoea, dysentery and cholera, and the fact established later that cholera germs do not develop in an aqueous extract of germinating barley. Hordenine is prepared by extracting air-dried malt with alcohol. Hordenine sulphate raises the blood pressure and increases the flow of urine. It is a remedy for diarrhoea and dysentery, and in general gives good results in cases where barley can be used with success.

On methylation by means of dimethyl sulphate, followed by oxidation with potassium permanganate in alkaline solution, hordenine is converted into anisic acid. When degraded by Hofmann's method it yields trimethylamine and *p*-vinylanisole, $\text{CH}_3\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH}_2$. The formula deduced in this manner has been confirmed by synthesis. Hordenine was first synthesised by Barger from phenylethyl alcohol, in the following stages :



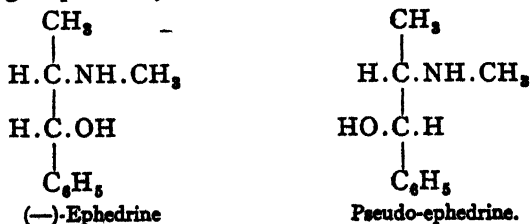
Mezcaline

From the cactus of the Anhalonium family, which grows in North America and is used by the natives as an intoxicant, a number of basic substances have been isolated, viz. several isoquinoline alkaloids, hordenine and mezcaline. The latter was shown by Späth to possess the following structure.



Ephedrine and Pseudo-ephedrine

The Chinese drug Ma Huang contains at least six bases, the most important of which are ephedrine and pseudo-ephedrine ; both bases also are found in *Ephedra vulgaris*. Ephedrine and pseudo-ephedrine are diastereoisomers which differ from one another in the configuration of the H.C.OH group. They are interconvertible.

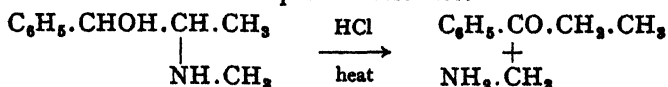


Ephedrine has pronounced mydriatic action ; it is a heart stimulant ;

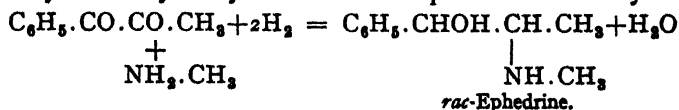
and as a result of its astringent action is used in hay-fever and asthma. Its structure has been proved by its chemical properties and syntheses. The presence of a benzene ring and side-chain is shown by oxidation to benzoic acid. The side-chain contains a secondary amino-group, since it gives a nitroso-compound with nitrous acid, and a hydroxyl-group which can be benzoylated. Ephedrine hydrochloride on heating undergoes *hydramine fission*, a reaction which is observed in compounds containing the $C_6H_5.CHOH.CH-$ fragment: propiophenone and



methylamine are formed in the present instance.



Of the several synthetic methods used, a particularly neat one is that in which benzoylacetyl is catalytically reduced in the presence of methyl-amine.¹

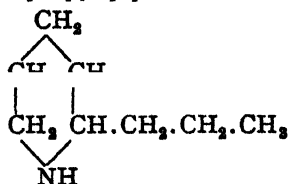


Doubt exists regarding the configuration of ephedrine and its isomer pseudo-ephedrine. Since (–)-ephedrine can be prepared from D(–), mandelic acid, the hydroxy-bearing carbon atom belongs to the D-series. Freudenberg² accordingly assigned the above formula to (–)-ephedrine, but Jarowski and Hartung³ have shown that the configuration of the amino-bearing carbon atom is not yet known.

II.—ALKALOIDS OF THE PYRIDINE GROUP

Among the large number of alkaloids containing a pyridine nucleus only coniine and piperine will be treated here.

α-Coniine, dextro-2-*n*-propyl-piperidine.



Coniine is of special interest from the historical standpoint, because the synthesis of this compound by Ladenburg, which was commenced in 1886 and finished at a later date, constituted the first complete synthesis of a naturally occurring alkaloid. The reason for the early synthesis of the compound lies in its simple constitution. Of the numerous alkaloids known to-day, very few are built up from carbon, hydrogen, and nitrogen alone, and of these coniine possesses the simplest structure.

¹ Skita and Keil, *Ber.*, 1929, 62, 1142. Manske and Johnson, *J.A.C.S.*, 1929, 51, 580.

² Freudenberg and Nikolai, *Ann.*, 1934, 310, 223.

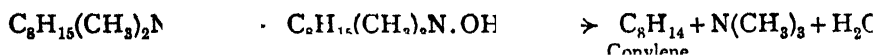
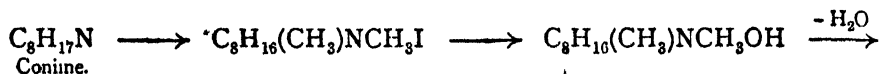
³ *J. Org. Chem.*, 1943, 8, 565. See also G. Fodor *et al.*, *ibid.*, 1949, 14, 337.

Coniine is present in hemlock, *Conium maculatum*, especially in the seeds, in which it is accompanied by N-methyl-coniine, γ -conicefine conhydrine, and pseudo-conhydrine. It is a colourless, very poisonous liquid, b.p. 167° .

Degradation of Coniine

A. W. Hofmann subjected coniine to certain reactions which he had previously carried out with piperidine, and found that the two compounds behaved in a similar manner.

1. *Exhaustive methylation* of coniine gave a product having the composition of a dimethyl-coniine, $C_8H_{15}(CH_3)_2N$, and also a hydrocarbon conylene, of the formula C_8H_{14} .



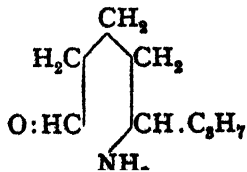
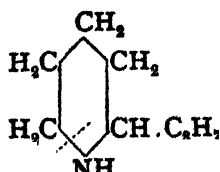
Hofmann observed that conylene differed from piperylene by the same atomic complex, C_8H_8 , as coniine from piperidine, and hence suggested that coniine might be a homologue of piperidine. Shortly afterwards, Königs put forward the surmise that coniine was a propyl-piperidine. This view was confirmed by Hofmann's distillation of the alkaloid with zinc dust.

2. The *distillation with zinc dust* was undertaken in the expectation of obtaining from coniine a compound richer in hydrogen. In actual practice it was found that hydrogen was removed and the compound $C_8H_{17}N$ converted into one of the composition $C_8H_{11}N$. The new base, *conyrine*, was easily recognised as a derivative of pyridine, and being six atoms poorer in hydrogen than coniine, appeared to stand to the latter in the same relationship as pyridine to piperidine.

Any doubt as to the nature of conyrine was resolved by its conversion into picolinic acid or 2-pyridine-carboxylic acid (see p. 719) on oxidation.

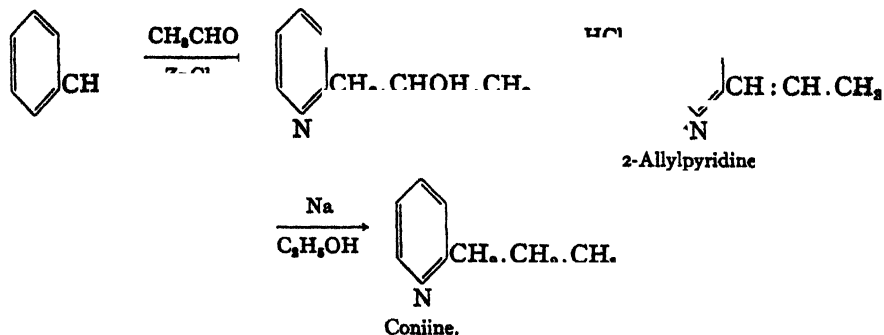
From this it followed that conyrine must be either 2-propyl- or 2-isopropyl-pyridine, and coniine therefore 2-propyl- or 2-isopropyl-piperidine. The choice between these two alternatives was decided in favour of the normal propyl structure by Hofmann's discovery that coniine, on reduction with hydriodic acid, gave ammonia and normal octane. Had an isopropyl group been present this could not have occurred without intramolecular rearrangement.

3. The *oxidation of coniine with hydrogen peroxide* led to the formation of δ -propyl- δ -aminovaleraldehyde (δ -amino-*n*-octoic aldehyde).



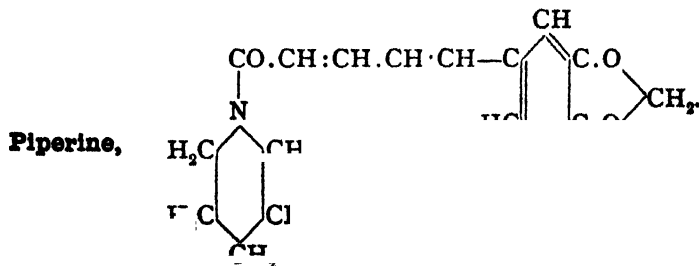
The constitution of coniine as 2-propyl-piperidine was finally confirmed by synthesis.

Synthesis of Coniine.—The synthesis of coniine, which is essentially that of Ladenburg (1889), is best effected by condensing α -picoline with paraldehyde and zinc chloride at 150° , the hydroxy product so obtained then being dehydrated by hydrochloric acid at 185° to 2-allylpyridine. This is reduced by sodium and alcohol to (L)-coniine.



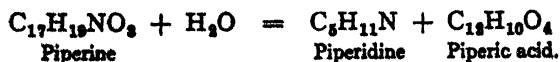
The racemic base may be resolved by means of (+)-tartaric acid. On crystallising a solution of γ -coniine (+)-tartrate the first salt to separate is (+)-coniine (+)-tartrate, which is then removed and decomposed with alkali.

Synthetic coniine thus obtained is identical in most respects with natural (+)-coniine, from which it differs mainly in possessing a slightly higher rotation (by about 4°).



The fruit and seeds of different species of pepper contain, in addition to a terpene, a comparatively large proportion (7 to 9 per cent.) of piperine. It was first discovered in 1819 by Oersted, and crystallises in monoclinic columns, m.p. 128° to 129°.

When boiled with alcoholic potash it breaks down into piperidine and piperic acid :

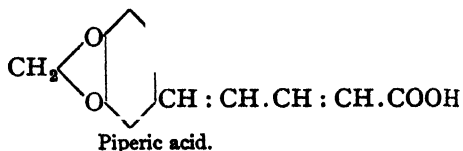
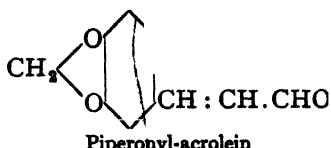
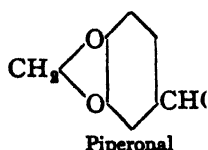


Hence it was concluded that piperine is a compound of amide type built up from piperidine and piperic acid. This view was confirmed by

the partial synthesis of piperine by heating piperidine in benzene solution with the chloride of piperic acid :

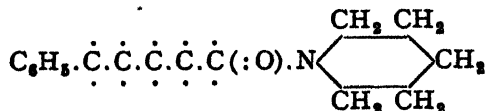


The constitution and synthesis of piperidine have been described on p. 720 *et seq.*, and the structure of piperic acid was solved by Fittig and confirmed by the following synthesis of Ladenburg and Scholtz. Piperonal (see p. 523) was condensed with acetaldehyde in the presence of aqueous alkali to give the unsaturated aldehyde, piperonyl-acrolein; the latter was then converted into piperic acid by use of Perkin's reaction.



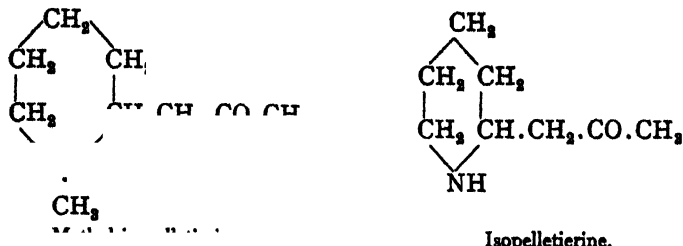
Consequently the above preparation of piperine from its hydrolysis products, piperidine and piperic acid, completes the synthesis of this alkaloid.

Owing to the rising price of pepper, experiments have been directed towards an artificial product of similar taste. An actual synthesis of piperine is out of the question owing to the cost of starting materials, but information as to the relationship between constitution and pepper-like taste has been gained by the work of H. Staudinger. It appears that the molecule of piperine may undergo considerable changes without losing the characteristic taste. An essential condition is the acid amide linking of piperidine with a fatty-aromatic acid radical, and the most pronounced resemblance to pepper was observed with derivatives of δ -phenyl-*n*-valeric acid. The most effective structure is thus the following

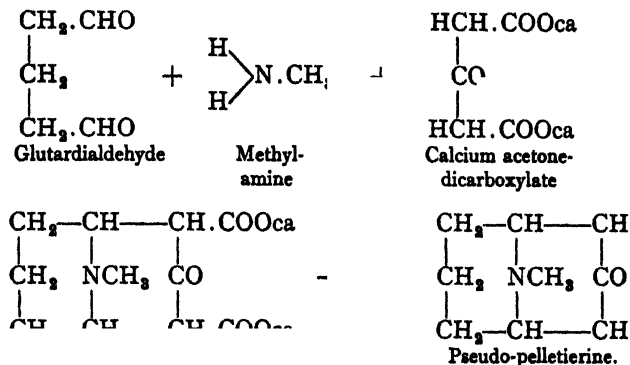


Alkaloids of the Pomegranate Bark.—The bark of the pomegranate tree (*Punica Granatum* L.) contains several alkaloids, to the presence of which is due its long-known usefulness as a vermicide. These alkaloids,

isopelletierine, *methylisopelletierine* (1-methyl-2-acetonyl-piperidine), and *pseudo-pelletierine* were examined in detail by Hess, and later by Meisenheimer. Their constitutions can now be regarded as established in accordance with the following formulae:



Pseudo-pelletierine was synthesised by Menzies and Robinson in a simple manner from glutaric aldehyde as follows (compare synthesis of tropinone, p. 755):



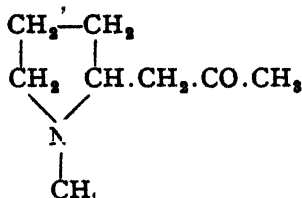
III.—ALKALOIDS OF THE PYRROLIDINE GROUP AND DERIVATIVES OF TROPANE

In this group are included hygrine and cuskhygrine, nicotine, atropine, hyoscyamine, cocaine, tropacocaine and others. Since the five-membered pyrrolidine ring is more easily formed than the corresponding six-membered ring, the production of alkaloids of the pyrrolidine type in plants is not surprising. In all probability a number of other alkaloids, the constitution of which is still unknown, will eventually be found to fall within this class.

Hygrines

From South American coca, obtained from truxillo and cusco leaves, Liebermann isolated two bases, hygrine ($C_8H_{15}NO$) and cuskhygrine ($C_{13}H_{24}N_2O$). Both of these are amino ketones, which on oxidation with chromic acid are converted into hygrinic acid (*cf.* p. 751).

Hygrine, 1-methyl-2-acetonyl-pyrrolidine, possesses the following structure :

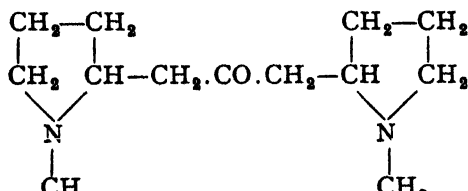


which is confirmed by the formation of a monoxime, the degradation of hygrine to hygrinic acid (1-methyl-pyrrolidine-2-carboxylic acid) (p. 751), and by the synthesis of the base.

Hygrine is found more particularly in Peruvian cusco leaves, in which it occurs up to 0.2 per cent. It is a liquid which darkens in air and boils at 193° to 195° under ordinary pressure.

Cuskhverine

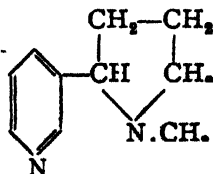
Cuskygrine, $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}$, is simply related to hygrine, $\text{C}_8\text{H}_{15}\text{NO}$, one hydrogen atom of the latter being replaced by the monovalent 1-methyl-pyrrolidine radical. It conforms in all probability to the structure



Cuskygrine is present in the crude hygrine obtained from cusco leaves, of which it constitutes the higher boiling main fraction. It is a colourless oil of faint odour, boiling at 185° under 32 mm. pressure.

Nicotine

1-Methyl-2-β-pyridyl-pyrrolidine,



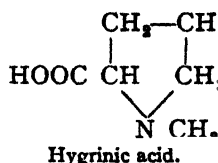
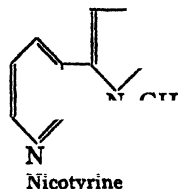
Nicotine is found combined with malic acid and citric acid in the leaves of tobacco (*Nicotiana tabacum*).

The above constitutional formula was advanced by Pinner in 1893.

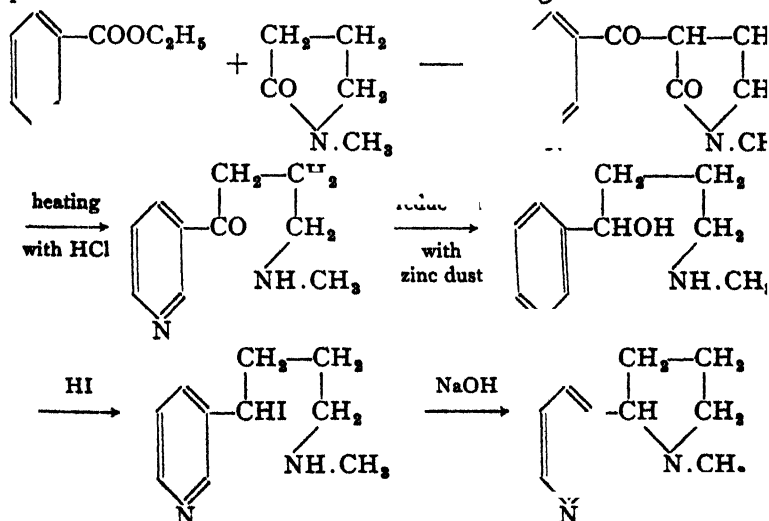
Constitution of Nicotine

Nicotine, $C_{10}H_{14}N_2$, is oxidised by many oxidising agents to nicotinic acid. It is therefore a derivative of pyridine with a $C_5H_{10}N$ group in the β -position. Now it is known that both nitrogen atoms in the alkaloid are tertiary and further that one of them is present as an N-methyl group. One of the nitrogen atoms occurs in the pyridine ring: the $N.CH_3$ group must therefore be part of the other half of the molecule, which accordingly consists of the fragment $C_4H_7.NCH_3$. This suggests that it is an N-methyl-pyrrolidine residue. This has been confirmed by the oxidation of nicotine to (—)-hygrinic acid, a reaction which also shows that the linkage to the pyridine ring occurs in the α -position of the pyrrolidine ring.

Mild oxidation of nicotine leads to dehydrogenation of the pyrrolidine nucleus to give *nicotyrine*. This compound occurs as an intermediate in the famous synthesis of nicotine by Pictet.¹ This synthesis, however,



involves drastic treatment at some stages with the attendant possibility of rearrangement. Much more conclusive is the synthesis effected by E. Späth and H. Bretschneider² in the following stages:



The first condensation in this synthesis is brought about in the presence of sodium ethoxide, giving a product which, on being heated with fuming hydrochloric acid, is hydrolysed with loss of carbon dioxide.

Nicotine has also been synthesised from pyridine by L. C. Craig.³

¹ Pictet and Rotschy, *Ber.*, 1904, 37, 1

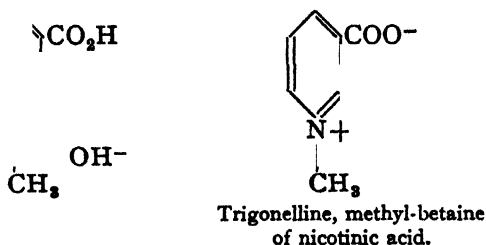
² *Ber.*, 1928, 61, 327.

³ *J.A.C.S.*, 15

(-)-Nicotine.—The naturally occurring alkaloid is laevorotatory, $[\alpha]_D^{20} = -166.4^\circ$, and can also be obtained by resolving the synthetic (\pm)-nicotine with the aid of tartaric acid. According to the kind of tobacco, the nicotine content varies from 0.6 to 8 per cent. (pipe tobacco 0.518 to 0.854 per cent., cigars 0.801 to 2.887 per cent.). In general the finer kinds of tobacco contain smaller proportions of nicotine.

Freshly prepared (-)-nicotine is a colourless oil, which dissolves readily in water, has a burning taste, and is very poisonous. When pure, it has an unpleasant, stupefying odour, unlike that of tobacco. Nicotine boils at 246.2° under 730 mm. pressure.

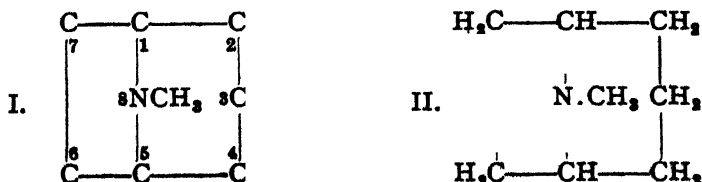
Nicotine yields two *mono-methiodides*. One of these isomerides is obtained as a syrupy mass on bringing together equimolecular amounts of nicotine and methyl iodide. The second results when nicotine is first treated with a molecular equivalent of hydriodic acid and then with methyl iodide: under these conditions the methyl iodide unites with the less basic nitrogen atom of the pyridine ring. By converting the methiodide into the hydroxide and oxidising the latter with potassium permanganate, Pictet obtained the alkaloid *trigonelline*, which is present in the seeds of *fenugreek*, of *Strophanthus hispidus*, etc., and in human urine.



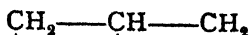
(-)-Nicotine is more poisonous than (+)-nicotine. In this respect, the different action of the two antipodes towards the animal organism may be compared to the different behaviour of optical antipodes in general towards any other optically active compound, and towards organised, as distinct from unorganised, ferments.

Compounds of the Tropane Series

Nomenclature.—The various alkaloids of this group contain a combination of a reduced pyrrole and a reduced pyridine ring (Willstätter), the periphery of the cyclic system forming a seven-membered carbon ring:



Derivatives of tropane are generally described by use of the numbering given in formula I, the compounds being referred in the customary manner to *tropane* (II) as parent substance. Tropane contains two asymmetric carbon atoms—C₁ and C₅—but as the molecule has a plane of symmetry tropane is optically inactive. It is a *meso*-compound.

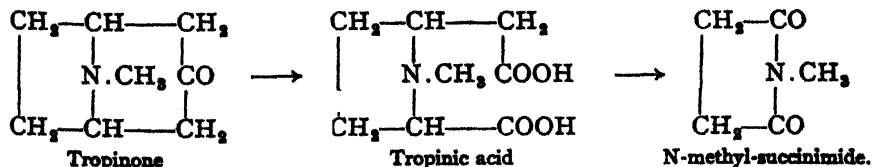


Tropine, m.p. 64-66°, the basic cleavage product of most of the Solanaceæ alkaloids (*e.g.* atropine), is one of the most important derivatives of tropane. It has been more completely investigated than any of the other derivatives, with results which gave the first insight into the structure of the tropane ring. Tropine was first obtained by the hydrolysis of atropine with barium hydroxide (Kraut, 1863), and was later isolated in a similar manner from hyoscyamine (Ladenburg) and belladonnine (Merling). Willstätter prepared tropine by the reduction of tropinone, and finally effected its synthesis.

Constitution of Tropine and Tropinone

The constitution of tropine was determined chiefly by Merling and Willstätter and rests mainly on the following evidence.

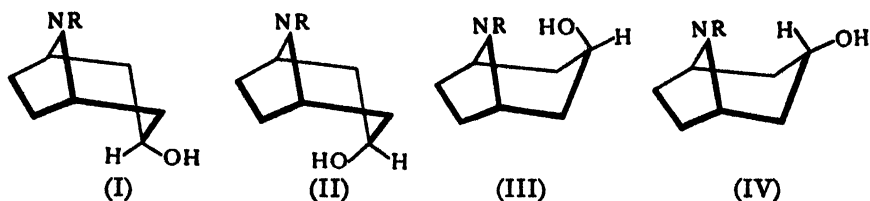
Tropine contains a N-methyl group and a secondary alcoholic group, since on oxidation it is converted into the ketone, **tropinone**. This ketone readily yields a dibenzal-compound and a di-isonitroso-derivative with benzaldehyde and nitrous acid respectively, and must therefore contain the group CH₂.CO.CH₂. Moreover, the carbonyl-group must be a member of a cyclic structure since tropinone on oxidation yields a dibasic acid *tropinic acid* (p. 664) with the same number of carbon atoms. Had the ketonic-group been in a side-chain an acid with a smaller number of carbon atoms would have resulted. Tropinic acid on energetic oxidation is converted into N-methyl-succinimide. In this way the presence of the pyrrolidine nucleus is established.



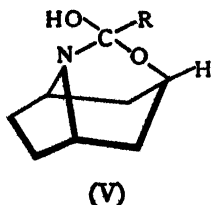
The formula for tropine and tropinone suggested by these and other reactions is given above and is confirmed both by the degradation (exhaustive methylation) of tropinic acid to an unsaturated dibasic acid

which on reduction gives pimelic acid and by Robinson's elegant synthesis of tropinone (p. 755) from which tropine is obtained by reduction. Robinson's simple synthesis has superseded the older and more complicated synthesis of Willstätter.

Reduction of tropinone with sodium and ethanol gives two epimerides, tropine and *pseudotropine* (ψ -tropine), the configurations of which have only recently been established. It is probable that in both compounds the piperidine ring occurs only in the chair form (p. 384), even though this form is only slightly more stable than the boat form. Now since it is known that reduction of carbonyl compounds such as tropinone by means of sodium and ethanol yields products with equatorial hydroxyl groups and since ψ -tropine is the chief product of reduction by this method it follows that ψ -tropine has the conformation I ($R = CH_3$). Tropine consequently has the conformation II ($R = CH_3$). In other words the hydroxyl group in ψ -tropine is *cis* with respect to the nitrogen atom, and in tropine it is *trans*. The closer proximity of the hydroxyl group to the nitrogen atom in ψ -tropine is shown by studies on *nortropine* (II, $R = H$) and *nor-ψ-tropine* (I, $R = H$) (compounds containing NH instead of NCH_3 as in the tropine series). N-benzoyl*nor-ψ-tropine* under the influence of hydrochloric acid is converted into O-benzoyl*nor-ψ-tropine*, whereas N-benzoyl*nortropine* does not undergo this change.¹ This difference between the behaviour of the two N-benzoyl compounds is readily understood if in the migration reaction N-benzoyl*nor-ψ-tropine*

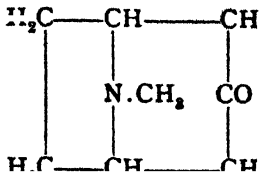


changes into the boat form (III, $R = CO.C_6H_5$).² The N-benzoyl and hydroxyl groups are now close enough for transference of the benzoyl group to occur. In the corresponding form of N-benzoyl*nortropine* (IV, $R = CO.C_6H_5$) the groups are widely separated and transference of the benzoyl group is sterically impossible. Final confirmation of the correctness of the assigned conformations is provided by the interaction of *nor-ψ-tropine* carbamate (III, $R = CO_2/2$) and *p*-nitrobenzaldehyde to give the oxazin (V, $R = p-NO_2.C_6H_4$)³ and by physical data.⁴



¹ G. Fodor and K. Nador, *Nature*, 1952, 169, 462. *J.*, 1953, 721. A. Nikon and L. F. Fieser, *J.A.C.S.*, 1952, 74, 5566. ² R. C. Cookson, *Chem. and Ind.*, 1953, 337. M. B. Sparke, *ibid.*, 1953, 749. A. K. Bose and D. K. R. Chaudhuri, *Nature*, 1953, 171, 652. ³ E. Hardegger and H. Ott, *Helv. Chim. Acta*, 1953, 36, 1186. ⁴ G. R. Clemo and K. H. Jack, *Chem. and Ind.*, 1953, 195. B. L. Zenitz, C. M. Martini, M. Priznar, and F. C. Nachold, *J.A.C.S.*, 1952, 74, 556.

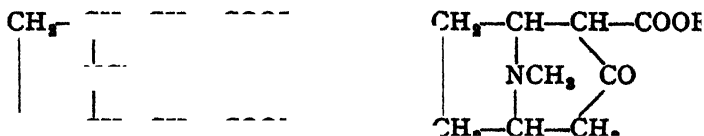
Tropinone (Tropanone)



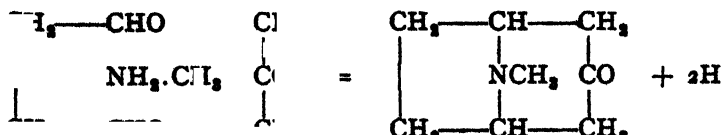
Tropinone, m.p. $41-42^\circ$, is the ketone corresponding to the alcohol tropine. It was obtained simultaneously by Willstätter and by Ciamician and Silber by the oxidation of tropine with chromium trioxide in glacial acetic acid solution, and results in a similar manner from ψ -tropine and from ecgonine. On further oxidation it yields tropinic acid.

Tropinone is best reduced to tropine by zinc dust and hydriodic acid in the cold. In this way a good yield of tropine, together with a smaller amount of ψ -tropine is obtained. Since tropinone can be obtained by the oxidation of ψ -tropine, it is thus possible to pass from ψ -tropine through tropinone into tropine, a change which cannot be effected in any other manner. Tropinone with sodium in moist ethereal solution is reduced to ψ -tropine, the same result being obtained by use of sodium amalgam in weakly acid solution.

The first *synthesis of tropinone* was carried out by Willstätter.

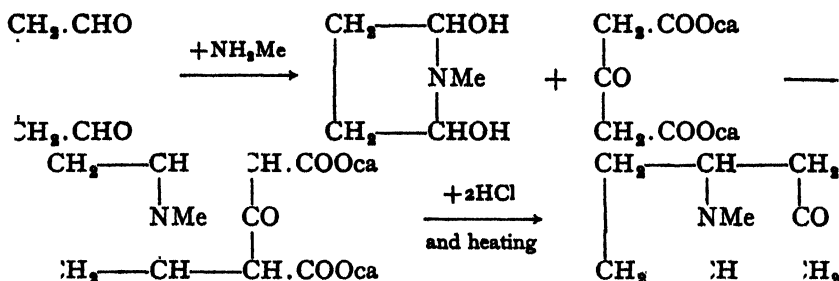


Robinson's synthesis of tropinone.—A remarkably simple synthesis of tropinone was devised by Robinson. Succindialdehyde was allowed to interact in aqueous solution with acetone and methylamine. After the lapse of half an hour at the ordinary temperature tropinone was found to be present.



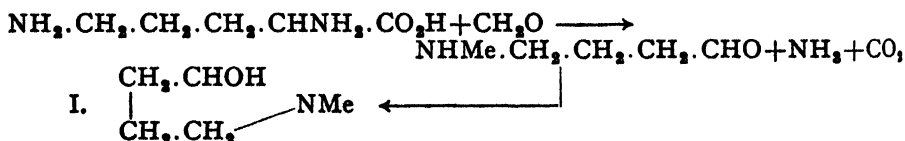
In an experiment in which the calcium salt of acetone dicarboxylic acid was employed in place of acetone, a yield of tropinone amounting to 42 per cent. of the theory was obtained. The tropinone dicarboxylate

first formed readily parts with two molecules of carbon dioxide on being heated in acid solution.

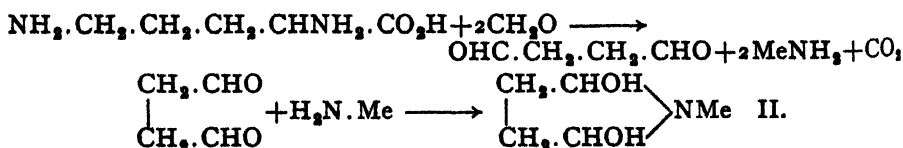


Robinson's Theory of the Phytochemical Synthesis of certain Alkaloids.¹—The synthesis of tropinone described above proceeds with such ease that Robinson has suggested that similar reactions probably occur in the plant. All new carbon to carbon links are assumed to result from (1) an aldol condensation, or (2) the closely related condensation between a compound containing the group :CH.CO. and a carbinol-amine having the group :C(OH).N:, products of the latter type being readily obtained by union of an aldehyde or ketone with ammonia or an amine (see II).

The essential starting points in the plant synthesis may be ammonia and formaldehyde, amino-acids such as ornithine or lysine, and certain degradation products of carbohydrates. For example, formaldehyde is known to exert a combined methylating and oxidising action on ornithine, leading to the loss of ammonia and carbon dioxide and the formation of a base which may undergo cyclisation to give a carbinol-amine (I) derived from pyrrolidine :



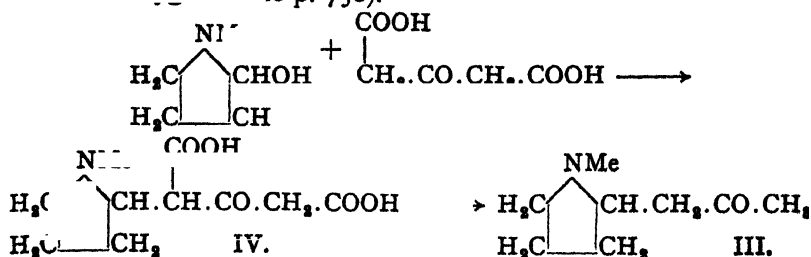
Further interaction with formaldehyde is supposed to attack both ends of the amino-acid molecule, yielding succindialdehyde and methylamine, which combine to form the dihydroxy base II.



Among carbohydrate disruption products, citric acid is suggested as providing acetone residues in the form of acetone-dicarboxylic acid. Alternatively, the latter compound is known to be produced *in vitro* from other sources, *e.g.* by the spontaneous decomposition of calcium tri-saccharate.²

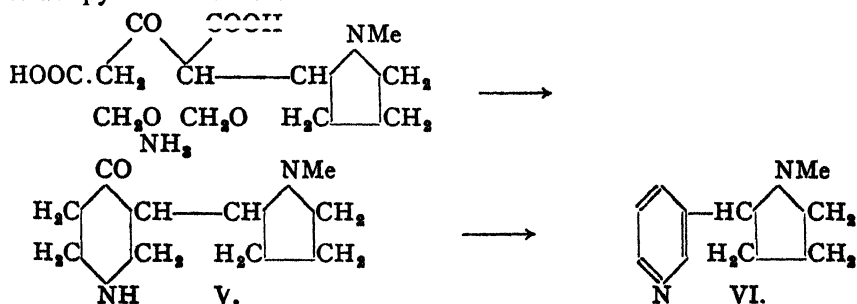
¹ R. Robinson, *J.*, 1917, 876. R. C. Menzies and R. Robinson, *J.*, 1924, 2163. Lippmann, *Ber.*, 1893, 26, 3057.

Condensation is then assumed to proceed along the following lines, according to which one molecule of acetone-dicarboxylic acid reacts with either one or two molecules of the base I. Subsequent elimination of carbon dioxide leads in the former case to **hygrine** (III), and in the latter to **cusckhygrine** (see p. 750).

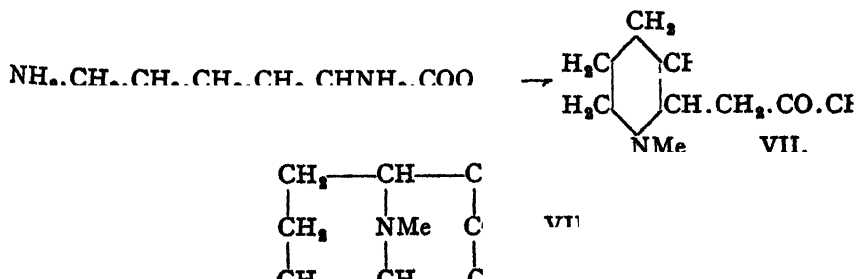


On the other hand, from the base II tropinone has already been synthesised in a similar manner, as described on p. 755. Tropinone by further simple changes in the plant may give rise to **tropine**, **ψ -tropine**, **hyoscyamine** and **atropine**.

Nicotine (VI) may be derived from IV, the immediate precursor of hygrine, by interaction with formaldehyde and ammonia, accompanied by loss of carbon dioxide. The ketonic ring in V is assumed to undergo reduction ($\text{CO} \rightarrow \text{CHOH}$) followed by dehydration ($\cdot \text{CH}_2 \cdot \text{CHOH} \cdot \text{CH} < \rightarrow \cdot \text{CH}_2 \cdot \text{CH} : \text{C} <$) and subsequent oxidation to the aromatic state. This mechanism clearly explains the β -attachment of the pyrrolidine ring to the pyridine nucleus.

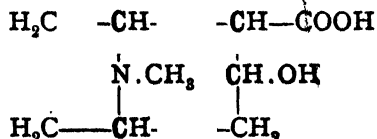


Piperidine derivatives would be expected to result by similar changes from the amino-acid lysine, which with formaldehyde should yield the **methyl-isopelletierine** VII and **ψ -pelletierine** (VIII). Both of these occur in the pomegranate tree



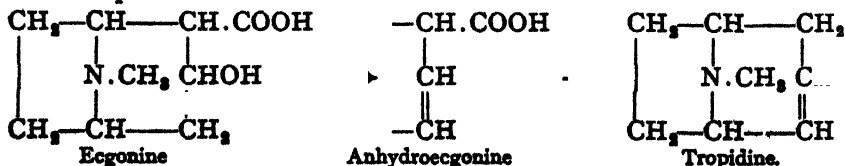
Robinson comments on the frequent occurrence in the same natural source of a number of closely related alkaloids, as in the case of the peltierines or of coniine and its associates. These variations, it is suggested, are produced from a primary product by alternate hydration and dehydration, or by oxidation and reduction. As an illustration it is observed that Hess has shown that the base VII reacts with formaldehyde in such a way that nitrogen is demethylated and the ketone reduced to the carbinol. The resulting compound on further reduction ($\text{CHOH} \rightarrow \text{CH}_2$) would yield **coniine** having the side chain $\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$; or by dehydration followed by hydration **conhydrine** might be formed ($\text{CH}_2 \cdot \text{CHOH} \cdot \text{CH}_2 \rightarrow \text{CH} : \text{CH} \cdot \text{CH}_2 \rightarrow \text{CHOH} \cdot \text{CH}_2 \cdot \text{CH}_2$). Similar considerations are advanced to account for the synthesis of other types of alkaloids, including *sparteine*, *cinchonine*, *hydrastine*, *narcotine*, *morphine* and *thebaine*.

Ecgonines, 3-Hydroxytropane-2-Carboxylic Acids



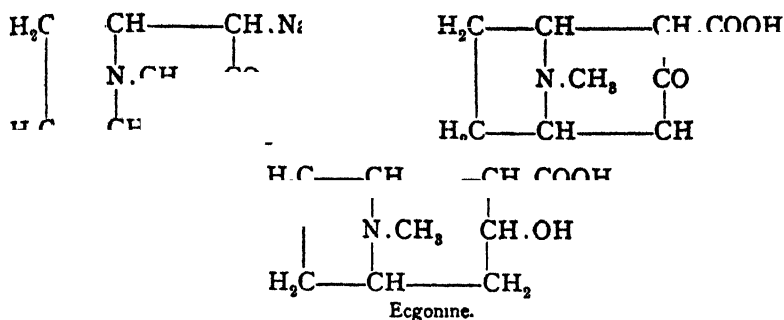
The ecgonines are 3-hydroxytropane-2-carboxylic acids, whose importance lies partly in their relationship to the cocaines, p. 763. They are amphoteric substances exhibiting the properties of amino-acids, and are capable of existing in various stereochemical modifications (see below). Before discussing these, however, it is necessary to consider the constitution of the ecgonines.

Ecgonine is a tertiary base which forms quaternary salts with alkyl halides, and contains a secondary alcoholic hydroxyl group since on oxidation it yields the ketone *tropinone*. With methanol it forms a methyl ester. Many of its reactions show its close relationship to tropine. With dehydrating agents it passes into an unsaturated acid, *anhydroecgonine*, which is decarboxylated on heating with hydrochloric acid at 280° to tropidine.



As already stated ecgonine on oxidation yields tropinone: further oxidation gives tropinic acid. The position of the carboxyl group is determined by the behaviour of the alkaloid, which shows the behaviour of a β - rather than of an α - or γ -hydroxy carboxylic acid. The presence of the two heterocyclic rings can be shown, since ecgonine when distilled with zinc dust yields 2-ethylpyridine and by means of suitable oxidation gives N-methylsuccinimide.

The structure thus assigned has been confirmed by synthesis. Sodium tropinone, suspended in ether, unites with carbon dioxide at room temperature to give sodium tropinone-carboxylate. This compound when reduced in cold, faintly acid solution with sodium amalgam yields two isomeric compounds, (\pm)-pseudoecgonine (ψ -ecgonine) and (\pm)-



ecgonine. The formation of these substances is probably due to the sodium tropinone reacting as the ketone salt (*cf.* acetoacetic ester) and thus yielding tropinone- β -carboxylic acid, which on reduction passes into ecgonine and ψ -ecgonine.

A second synthesis, also effected by Willstätter, is the reduction of methyl tropinone-2-carboxylate, which yields three products: (1) (\pm)- ψ -ecgonine methyl ester, (2) (\pm)-ecgonine methyl ester, and (3) a third racemic ecgonine.

Ecgonine, as will be seen from the formula, contains four asymmetric carbon atoms and should therefore exist in 16 optically active forms. As, however, the $-\text{CH}_2-\text{CH}_2-$ bridge united to the piperidine ring can only be attached in the *cis*-position, the number of possibilities is reduced to eight. The configurations of the four parent racemic compounds are determined by the positions of the hydroxyl group and carboxyl group relative to that of the N-methyl group in the non-planar molecule (*cf.* the non-planar tropine molecule). The four compounds thus contain, relative to the N-methyl group the following groupings: *cis*-OH, *cis*-COOH. *cis*-OH, *trans*-COOH. *trans*-OH, *cis*-COOH. *trans*-OH, *trans*-COOH. There is evidence that ecgonine contains the *cis*-OH, *cis*-COOH configuration, and ψ -ecgonine the *cis*-OH, *trans*-COOH configuration.¹

Alkaloids of the Tropane Series

To this group belong the alkaloids of the Solanaceæ and the coca alkaloids.

1. ALKALOIDS OF THE SOLANACEÆ

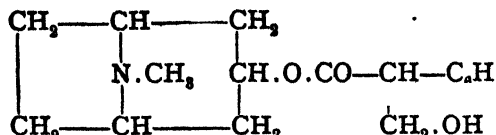
In many members of the Solanum family, such as *Atropa belladonna* (Deadly Nightshade), *Datura stramonium* (Thorn apple), *Hyoscyamus niger* (Henbane), are found a number of alkaloids closely related to

¹ S. P. Findlay. *J.A.C.S.*, 1952, 74, 4624. *cf.* F. Fodor and O. Kovacs, *J.*, 1953, 724.

each other in their properties and chemical constitution. Chief among these are two isomerides of the composition $C_{17}H_{23}NO_3$, viz., optically inactive *atropine* and laevorotatory *hyoscyamine*.

Atropine is the racemic modification of hyoscyamine.

Atropine, tropine ester of (\pm)-tropic acid



This compound occurs in the Deadly Nightshade (*Atropa belladonna*), in *Datura stramonium*, and in the root of *Scopolia japonica*.

Atropine, m.p. 115° to 116° , is optically inactive and has a sharp and bitter taste. It is a strong poison. Owing to its property of dilating the pupil of the eye (mydriasis) it is extensively employed in medicine. Atropine has assumed increased importance since it is the only known antidote to nerve gases.

Atropine results from the racemisation of its optical-isomeride hyoscyamine, (1) when the latter is heated to 110° in absence of air, (2) on being treated in alcoholic solution with a few drops of alkali, or (3) spontaneously in the course of time.

When treated with nitric acid, and also when warmed with acetic or benzoic anhydride, or phosphorus pentoxide, atropine loses a molecule of water and yields *apoatropine*, $C_{17}H_{21}NO_2$, which has been found to be identical with the naturally occurring *atropamine*. The latter crystallises in prisms, m.p. 60° to 62° , and was shown to be an ester of tropine and atropic acid, $C_8H_5 \cdot C \cdot \text{COOH}$. If atropine is heated to 130° it

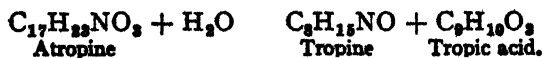


loses water in another manner and a certain proportion is converted into *belladonna*, an uncrystallisable mass with the appearance of varnish.

Atropine sulphate, $(C_{17}H_{23}NO_3)_2H_2SO_4 + H_2O$, is employed in eye surgery.

Constitution and Synthesis of Atropine

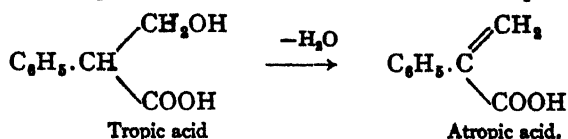
In 1863 Kraut discovered that atropine, on being boiled with aqueous baryta, decomposed to yield *tropine* and *atropic acid*. A year later it was shown by Lossen that the primary product of decomposition was not atropic acid, $C_9H_9O_3$, but *tropic acid*, $C_9H_{10}O_3$, and that the latter was then converted into the former by loss of 1 mol. water. Consequently the change undergone by atropine is merely the hydrolysis of an ester into acid and (basic) alcohol.



By reversing the above process Ladenburg, in 1879, effected a partial synthesis of atropine. On treating tropine tropate with hydrochloric acid he succeeded in regenerating atropine, thus proving it to be the tropine ester of tropic acid.

The problem of the constitution of atropine therefore resolved itself into two parts: the study of tropic acid and that of tropine.

As stated above tropic acid readily loses a molecule of water to give the unsaturated acid, *atropic acid*. This behaviour, characteristic of a β -hydroxy-acid points to the annexed formula for tropic acid.

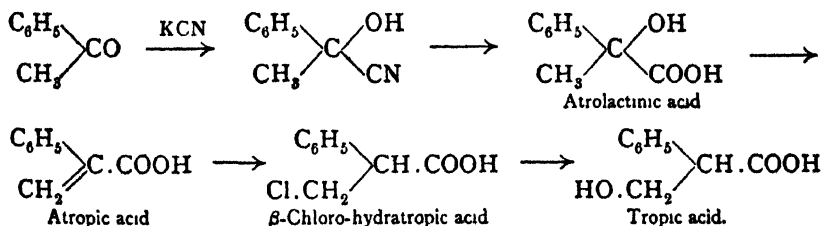


This structure has been confirmed by several syntheses.

Phenylacetic ester, $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$, is condensed with formic acid to give *formylphenylacetic ester*. This on reduction with aluminium amalgam yields *tropic ester*.



Another method of preparing this acid is that of McKenzie and Wood. Acetophenone is converted into atrolactic (atrolactinic) acid, which on being heated under diminished pressure gives atropic acid. The latter unites with HCl in ethereal solution to form β -chlorohydratropic acid, which finally yields tropic acid on being boiled with aqueous sodium carbonate.



The presence of an asymmetric carbon atom in tropic acid indicated the possibility of resolving the acid into its active components and thus of preparing optically active atropines. The resolution of tropic acid was effected by Ladenburg by means of the quinine salt, and from the active components the *active atropines* were then built up. By using other acids in place of tropic acid Ladenburg prepared other esters of tropine, to which he gave the collective name of *tropines*.

The structure of the alcohol tropine, the remaining hydrolysis product of atropine has been described in detail on p. 753 *et seq.*

Homatropine, $\text{C}_{16}\text{H}_{21}\text{NO}_3$, m.p. $95.5^\circ\text{--}98.5^\circ$, is by virtue of its physiological action the most important compound of the tropine group after

atropine and hyoscyamine. It is prepared from tropine and mandelic acid. In the form of its hydrobromide, homatropine possesses almost as powerful an action in dilating the pupil of the eye as atropine, but the effect disappears comparatively rapidly. It behaves similarly with respect to the paralysis of the power of accommodation. Homatropine is a much weaker poison than atropine and is also used in eye surgery.

Atropine, homatropine, and their salts are now obtained commercially by synthesis as well as from natural sources.

Hyoscyamine, (—)-Tropic Ester of Tropine

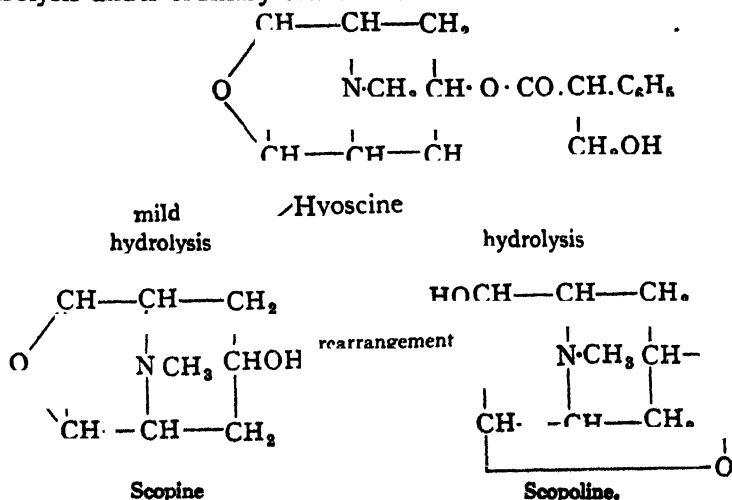
Hyoscyamine was first prepared from henbane, and occurs also in a number of other plants. It was found by Dunstan and Brown in *Hyoscyamus muticus*, and by Thoms and Wentzel in mandragora root.

It crystallises from alcohol in needles, m.p. 108.5° , and resembles atropine in its sharp, penetrating taste and mydriatic action. The main difference between these two alkaloids lies in the laevorotation of hyoscyamine as compared with the optical inactivity of atropine.

Hyoscyamine can be synthesised by stages similar to those used in the case of atropine (p. 761), the final combination being with (—)-tropic acid in place of the racemic compound. Natural (—)-rotatory hyoscyamine has about a hundred times greater physiological activity than the (+)-form.

Dehydrating agents convert hyoscyamine into *atropamine* and *belladonnine*. These alkaloids are also obtained in the same way from atropine.

Hyoscine or scopolamine, $C_{17}H_{21}NO_4$, is also found in plants of the Solanaceæ family. It is the ester of the amino alcohol *scopine* with (—)-tropic acid. Scopine is obtained on mild hydrolysis but readily undergoes rearrangement to *scopoline* (*oscine*), which is the product obtained by hydrolysis under ordinary conditions.



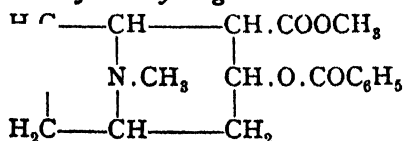
The physiological action of hyoscine is sedative, without the deleterious secondary effects of atropine. In mydriatic action the alkaloid is many times more powerful than atropine. "Twilight Sleep" is a mixture of hyoscine and morphine.

2. THE COCA ALKALOIDS

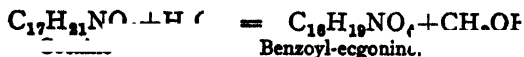
Cocaine

The leaves of *Erythroxylon coca* contain a large number of alkaloids, including the hygrines, already described on p. 749 *et seq.* and (—)-cocaine. Of the coca alkaloids (—)-cocaine is the most valuable and important. It is highly prized as a local anæsthetic and, owing to the short length of time during which it is operative, is largely used in eye surgery and dentistry. It is employed in the form of its hydrochloride and cannot be used for producing prolonged anæsthesia on account of its poisonous properties. Instead of the alkaloid cocaine substitutes are now very frequently used (see p. 764).

Cocaine, methyl ester of benzoyl-ecgonine.



(—)-Cocaine, m.p. 98°, was first isolated by Niemann in 1860 from Peruvian coca leaves (*Erythroxylon coca*). Its structural relationship to ecgonine is demonstrated by hydrolysis. Hydrolysis with boiling water yields methanol and benzoyl-ecgonine.

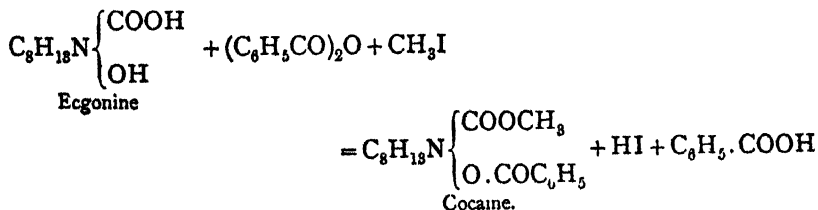


More powerful hydrolysis by means of mineral acids, baryta water or caustic alkali results in the benzoyl-ecgonine undergoing further decomposition into (—)-ecgonine and benzoic acid.



These reactions led to the conclusion that cocaine is the methyl ester of benzoyl-(—)-ecgonine, and prepared the way for its preparation from ecgonine.

A partial synthesis of (—)-cocaine was first effected by Merck, by heating (—)-ecgonine with benzoic anhydride and methyl iodide.

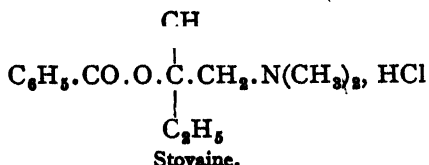


Cocaine is also obtained in good yield when (—)-ecgonine is treated in concentrated aqueous solution with benzoic anhydride, and the benzoyl-(—)-ecgonine so obtained esterified by methanol in the presence of

hydrochloric or sulphuric acid. Since considerable quantities of (—)-ecgonine can be prepared from the therapeutically valueless alkaloids found with natural cocaine the above method of increasing the supply of (—)-cocaine is of special importance.

It is to be anticipated that cocaine can exist in four stereochemical isomeric forms (*cf.* ecgonine), each capable of resolution into two optical isomers. Two of these, (—)-cocaine and (+)-pseudococaine, occur in coca leaves.

Cocaine substitutes.—Cocaine is a valuable therapeutic agent, but has serious disadvantages. It is toxic and produces a condition of euphoria which may give rise to addiction. As a result many substitutes have been synthesised. Two of the most successful of these, novocaine and tutocaine, have already been mentioned on p. 529. Percaine, a derivative of 2-hydroxyquinoline-4-carboxylic acid, has also been discussed (p. 731). Other substitutes are **stovaine**, which is less toxic than



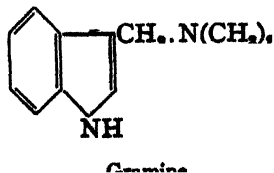
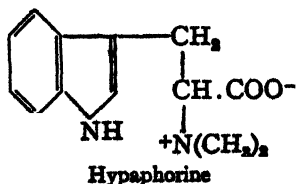
cocaine and **psicaine** ((+)-pseudococaine acid tartrate). Stovaine is widely used for intraspinal injections.

Other synthetic products such as eucaine and β -eucaine are no longer used.

IV. ALKALOIDS OF THE INDOLE GROUP

In this class are included many important alkaloids among the more complicated of which may be mentioned physostigmine, yohimbine, and the *strychnos* alkaloids strychnine, brucine, and vomicine (see p. 774), and the ergot alkaloids such as ergotoxine, ergotaminine. Only a brief account of some of the simpler members can be given here.

Two alkaloids containing only an indole nucleus are *hypaphorine* and *gramine*. It has been suggested that such compounds are derived in nature from tryptophan, and in support of this it may be pointed out that hypaphorine is the methylbetaine of tryptophan.



nitric acid yields isonicotinic acid. The fact that no trace of the more stable isomeric acid, nicotinic acid, is found shows that there is no carbon atom attached to the β -position of the pyridine ring.

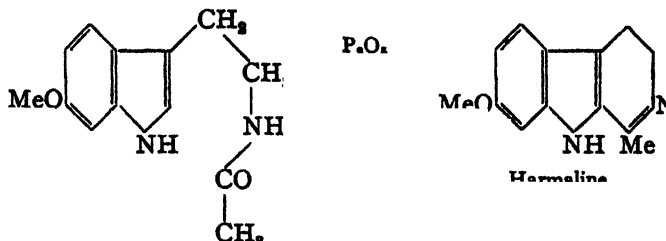
(b) *Presence of a reactive methyl-group.*—The presence of a methyl group which in all probability is ortho or para to the nitrogen of the pyridine ring (*cf.* p. 716) is shown by the condensation with benzaldehyde to give a benzylidene derivative. Harman (obtained by the demethoxylation of harmine), for example, gives a derivative which by oxidation and decarboxylation (heating in glycerol) gives *norharman* (*nor* meaning methyl-free).

(c) The presence of a *secondary nitrogen atom* is shown by acetylation, etc.

(d) *Presence of a methoxy-substituted benzene ring* is shown by the nitric acid oxidation of harmaline to give *m*-nitroanisic acid.

(e) Strong evidence for the central *pyrrole nucleus* is provided by the red dye-stuffs obtained through the action of diazonium salts on the alkaloids.

Finally various syntheses confirmed the structures advanced, and established the positions of the methyl group and the ethylenic bond in harmaline. For instance, Späth and Lederer effected an unambiguous synthesis of harmaline, by acetylating β -6-methoxyindolyethylamine and ring-closing the product by heating with phosphorus pentoxide.



V. ALKALOIDS OF THE QUINOLINE GROUP

In this section are included the important Cinchona bases, quinine and cinchonine, together with the Strychnos bases, strychnine and brucine.

Quinine and Cinchonine

Cinchona or Peruvian bark, which has been used in Europe since the middle of the seventeenth century in the treatment of fevers, is obtained from various trees of the Cinchona family found mainly in Bolivia and Peru. It contains, in addition to a tannin and quinic acid, a series of alkaloids which are closely related to one another in structure. The most important of these are *quinine*, $C_{20}H_{24}N_2O_8$, to which the curative action of the bark is chiefly due, and *cinchonine*, $C_{19}H_{23}N_2O$.

Quinine generally crystallises with 3 mols. H_2O , and in the anhydrous condition melts at 177° ; it separates from alcohol and ether in shining needles and is laevorotatory. It is present in yellow calisaya bark to the extent of 2 to 3 per cent., has an alkaline reaction, a bitter taste, and as a diacid base forms neutral and acid salts. Quinine is one of the most valuable medicines, especially in the treatment of intermittent fevers such as malaria and swamp fever, and is an antidote against many infections caused by micro-organisms.

Cinchonine accompanies quinine and is found in particularly large amounts in grey cinchona bark (*Cinchona Huanaco*), in which it occurs up to 2.5 per cent. It crystallises from alcohol in white prisms, sublimes readily, melts at 264° and is dextrorotatory. As a febrifuge it is less active than quinine.

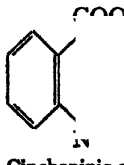
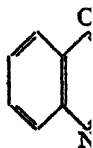
Quinine and cinchonine are similarly constituted, and therefore the results obtained by the investigation of these compounds have often supplemented one another. In many cases information gained with regard to cinchonine has been applied without modification to quinine.

Both alkaloids were discovered in the year 1820 by Pelletier and Caventou, and their constitutional formulæ have been deduced from evidence gradually accumulated from a large number of investigations in which Skraup, Königs, and Rabe took a leading part.

Cinchonine

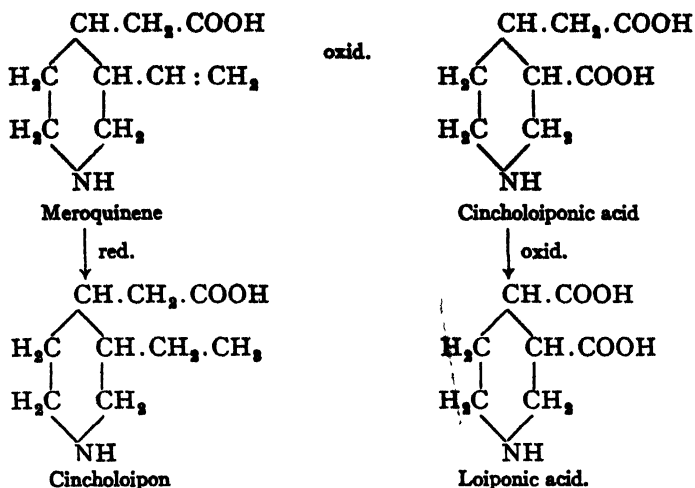
As already stated the composition of cinchonine is $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}$. The presence of a hydroxyl group and two tertiary nitrogen atoms in cinchonine is shown by the standard tests. The molecule absorbs one molecule of hydrogen in presence of a catalyst showing the alkaloid possesses one double bond. The oxygen is present in a secondary alcohol group, since on oxidation cinchonine yields a ketone, *cinchoninone*.

Various forms of degradation show that cinchonine is a quinoline derivative. With concentrated potassium hydroxide quinoline and lepidine (4-methylquinoline) are obtained. More information is obtained by oxidation with a solution of chromic acid in sulphuric acid when *cinchoninic acid*, quinoline-4-carboxylic acid, is obtained.



Cinchonine clearly is a quinoline derivative joined in the 4-position
 o what was described by Skraup as the "second half" of the molecule,

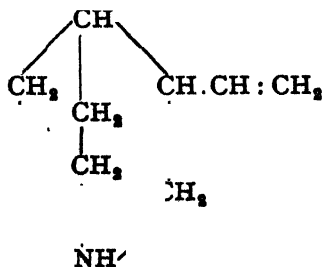
Constitution of the "Second Half" of Cinchonine.—The most important clues to the structure of the second half were furnished by oxidation. Three acids were obtained—*loiponic acid*, *cincholoiponic acid*, and *meroquinene*.



The structures of these compounds were determined by oxidation and synthesis. Meroquinene, when oxidised with an ice-cold aqueous solution of potassium permanganate and sulphuric acid, yields the dibasic acid, cincholoiponic acid. This acid on dehydrogenation and decarboxylation with sulphuric acid gives γ -picoline (4-methylpyridine), and on oxidation loiponic acid the structure of which was proved by synthesis. Hence meroquinene, cincholoiponic acid, and loiponic acid represent successive stages in the oxidation of the second half of quinoline.

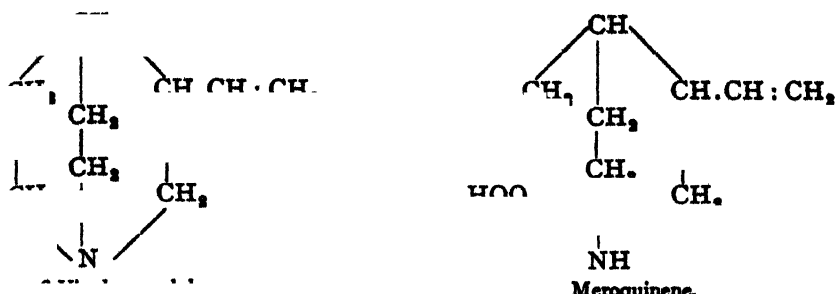
Meroquinene on oxidation gives not only cincholoiponic acid but also formic acid. This indication of the presence of a vinyl group in the molecule is confirmed by reduction to *cincholoipon*, the vinyl group being reduced to the ethyl group.

These facts show that the "second half" contains a piperidine nucleus

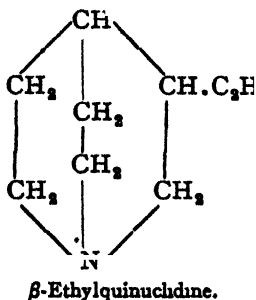


with a vinyl group attached in the β -position to the nitrogen, and a methylene group in the γ -position. Meroquinene, etc., however, have secondary nitrogen atoms, while both nitrogen atoms in cinchonine are

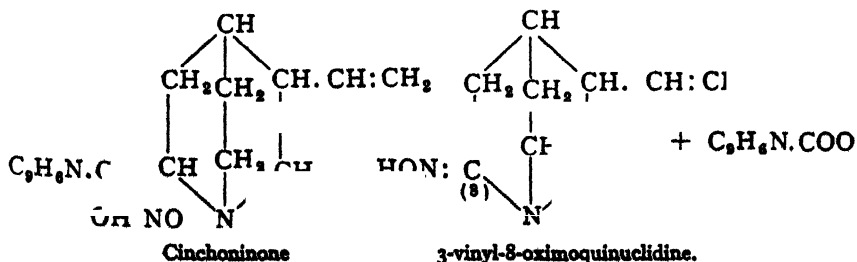
tertiary. The carboxy and secondary amino groups of meroquinene must be due to the fission of a carbon-nitrogen linkage. For instance :



The possibility of the existence of a quinuclidine structure with a carbon bridge between the nitrogen atom and the 4-carbon atom of the piperidine nucleus was established by the synthesis of β -ethyl-quinuclidine of the annexed structure (Königs). The parent compound has also been obtained

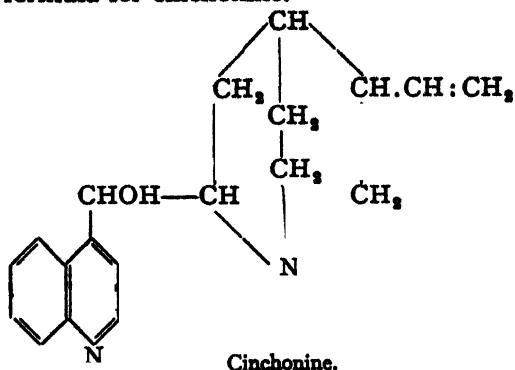


There only remains to be determined the mode of union of the two "halves" of cinchonine. This was shown by Rabe who found that the ketone cinchoninone with a reactive CH group adjacent to a carbonyl group yields with nitrous acid cinchoninic acid and an oxime, 3-vinyl-8-oximequinolidine.



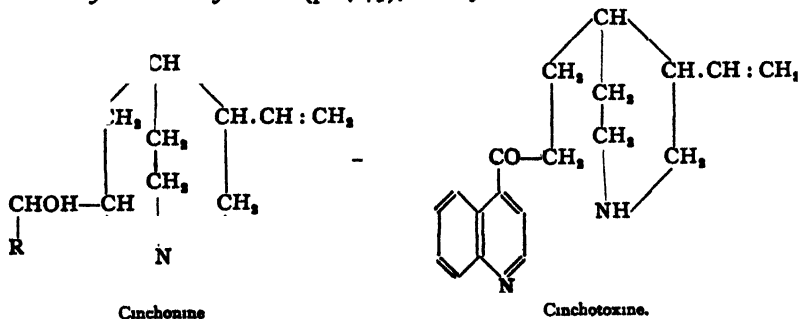
The structure of the oxime was shown by hydrolysis to hydroxylamine and meroquinene. The quinuclidine portion is therefore linked to the quinoline portion by a CHOH group attached to the 8-carbon atom.

The investigations described in the foregoing pages led to the adoption of the following formula for cinchonine.

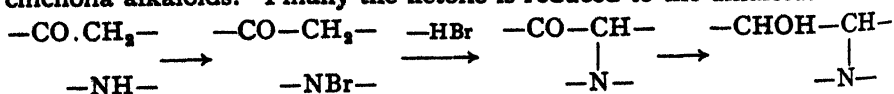


Since this formula contains 4 asymmetric carbon atoms, 16 optically active and 8 racemic stereo-isomerides are possible. Among these are *cinchonidine*, which gives the same fission products as cinchonine.

Partial Synthesis of Cinchonine.—Like other cinchona alkaloids cinchonine undergoes isomeric change. For example, when heated for a long time with acetic acid, it undergoes a remarkable molecular change known as *hydramine fission* (p. 745), and yields the ketone cinchotoxine.¹



The $-\text{CHOH}$ group is converted into $-\text{CO}-$, accompanied by rupture of the quinuclidine nucleus. A partial synthesis of the alkaloid by reversing the process has been effected through the following stages. The hydrogen atom of the imino group of cinchotoxine can be replaced by bromine to give a bromo-imine, which by loss of a molecule of hydrogen bromide is converted into cinchoninone (see p. 769). These reactions lead to the regeneration of the quinuclidine nucleus peculiar to the cinchona alkaloids. Finally the ketone is reduced to the alkaloid.

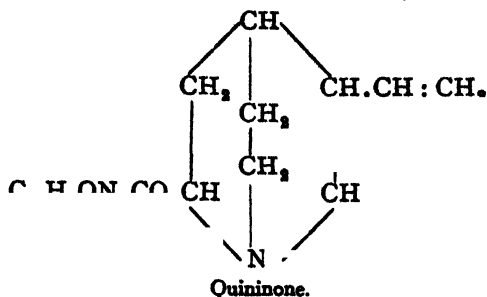


By this method the *toxines* (so called because of their poisonous properties) are converted back into the parent compounds, and among the partial syntheses so effected is that of quinine (see p. 771).

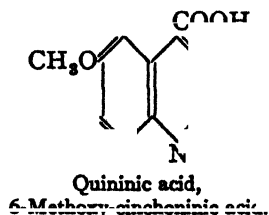
¹ P. Rabe and Schneider, *Ann.*, 1909, 365, 377.

Quinine

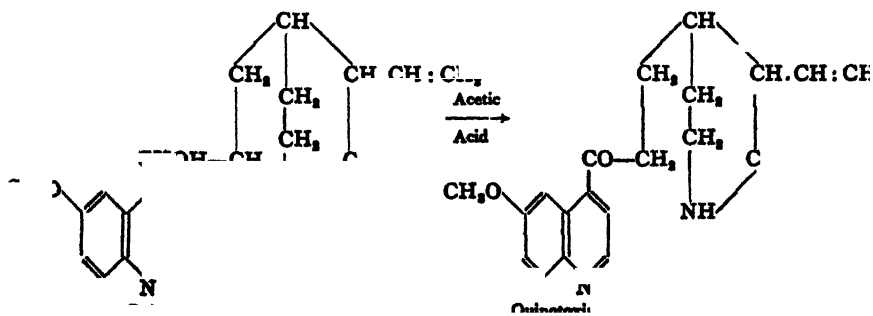
As has already been pointed out, much of our knowledge of the structure of quinine comes from investigations on cinchonine. Quinine differs from cinchonine only by its possession of a methoxy group, and is, indeed, a methoxycinchonine. Its secondary alcohol group can be



oxidised to give the ketone, *quininone*. The "second half" of quinine is identical with that of cinchonine: consequently the methoxy group must be present in the quinoline nucleus. This was shown to be the case and, in addition, the position of the methoxy group was determined by energetic oxidation of quinine with chromic acid, when *quininic acid* was obtained. Quinic acid was shown by Skraup to be 6-methoxycinchoninic acid: it was synthesised by Rabe and co-workers.



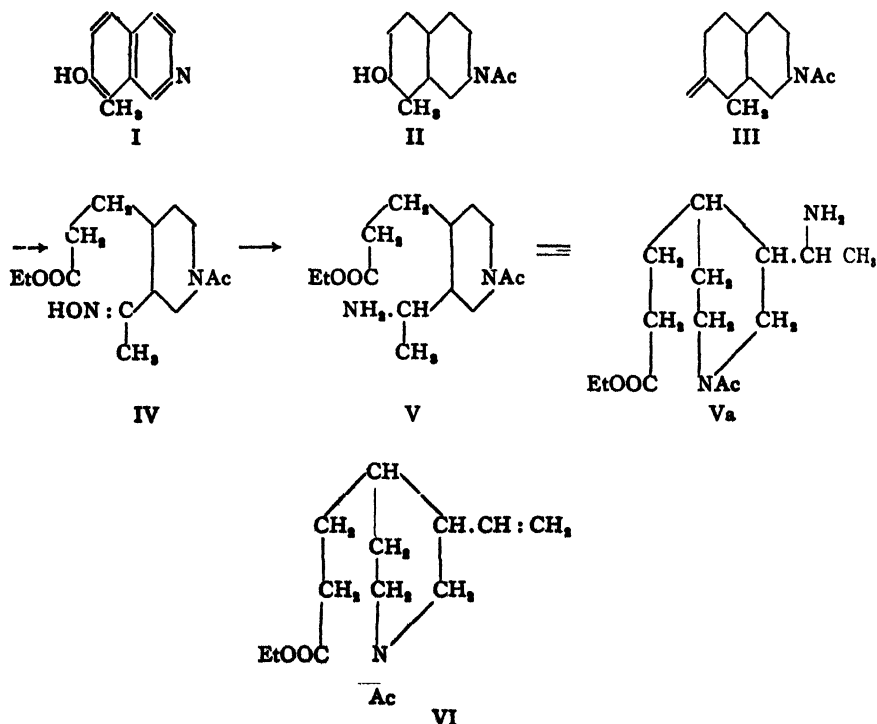
Quinine is therefore represented by the formula given below which was first advanced by Rebe in 1808



Synthesis of Quinine.—Quinine, like cinchonine, when heated with acetic acid undergoes hydramine fission and *quinotoxine* is obtained. By a method similar to that applied to cinchotoxine, Rabe achieved

partial synthesis of quinine from quinotoxine. The synthesis of quinine, therefore, really developed into a synthesis of quinotoxine. The brilliant pioneer work of Rabe has recently been successfully completed in a notable achievement by R. B. Woodward and W. E. Doering¹ who synthesised quinotoxine by the series of reactions outlined below. The synthesis involves many stages and only the briefest outline can be given here.

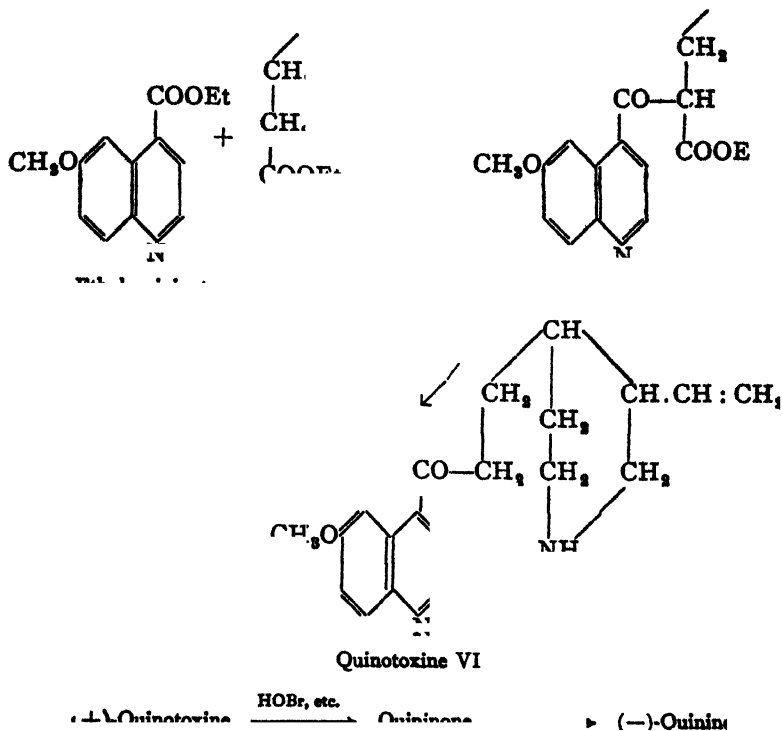
7-Hydroxy-8-methylisoquinoline (I) is reduced to a mixture of stereoisomeric compounds from which *cis*-N-acetyl-7-hydroxy-8-methyl-decahydroisoquinoline (II) is isolated (the *cis*-configuration refers to the hydrogen atoms on the two carbon atoms common to both rings). Oxidation yields the ketocompound (III) which forms with sodium ethoxide and ethyl nitrite an oximino-ester (IV), fission of one ring occurring in the process. Reduction results in formation of an amine (V and Va) which on exhaustive methylation gives the ethyl ester of acetyl-(±)-homoquinene (VI).



(±)-Homoquinene in the form of the benzoyl derivative of the ethyl ester condenses with the ethyl ester of quinic acid, the keto-ester so formed on ketonic hydrolysis (*cf.* acetoacetic ester) giving (±)-quinotoxine (VII).

¹ *J.A.C.S.*, 1944, 66, 849.

(+)-Quinotoxine, obtained by resolving the racemic compound with dibenzoyl-(+)-tartaric acid, is a yellow oil, and from it quinine is obtained by Rebe's method.



Compounds related to Quinine.—Quinidine, $\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2$, is a stereoisomeride of quinine to which it is related as cinchonidine is to cinchonine (see p. 770). It is dextrorotatory and melts at 171°C .

Hydroquinine, $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}_2$, is similar in structure to quinine, except that it has an ethyl group instead of the vinyl group. It is obtained from quinine by catalytic hydrogenation.

Demethylated quinine—the derivative of 6-hydroxy-quinoline corresponding to quinine—is found in a bark obtained from *Remija pedunculata*. This alkaloid is known as cupreine, and on methylation is converted into quinine. Thus quinine is the methyl ether of cupreine, to which it is related as codeine is to morphine. Hydrocupreine is obtained by demethylation of hydroquinine with hydrochloric acid at 150°C . The higher homologues of hydrocupreine have a strong disinfectant action towards pathogenic bacteria. *Eucupine*, the hydrochloride of iso-amyl-hydrocupreine, and *vusine*, or iso-octyl-hydrocupreine, are commercial products. Eucupine also possesses an anæsthetic action.

The Strychnos Alkaloids

The alkaloids of *Strychnos nuxvomica* and of Ignatius beans (*S. Ignatii*) are strychnine, brucine, and vomicine. To unravel the complicated chemical reactions of these compounds and derive adequate formulæ have entailed decades of intensive research particularly by Leuchs, Wieland, and Robinson.

Strychnine occurs in Ignatius beans (the seeds of *Strychnos Ignatii*), in the seeds of the fruit of *Strychnos nux vomica*, and in other sources.

It crystallises in rhombic prisms, which melt at 284° . It is very insoluble in water, has a bitter metallic taste, and is one of the most powerful poisons known. Regnault showed that the empirical formula of strychnine is $C_{21}H_{22}O_4N_2$.

Leuchs and Robinson have proposed formulæ for strychnine and brucine.¹

Brucine, $C_{22}H_{26}O_4N_2$, is generally found with strychnine in the wood and seeds of the various strychnos plants.

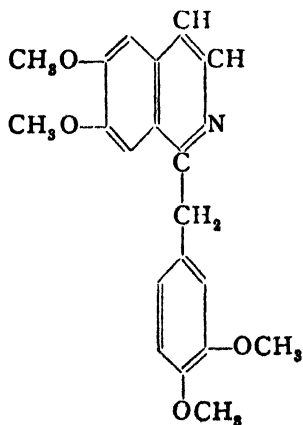
Brucine has the same physiological properties as strychnine, but is much less active. It is a dimethoxy derivative of strychnine.

VI.—ALKALOIDS OF THE ISOQUINOLINE GROUP

This group includes the five opium alkaloids, papaverine, laudanoline, laudanine, narcotine and narceine. These are 1-benzylisoquinoline derivatives the first three being comparatively simple substances.

When it is remembered that the alkaloids hydrastine and berberine found in the root of *Hydrastis canadensis* are also derived from isoquinoline, the importance of the latter as a parent compound of alkaloid bases becomes obvious.

Papaverine, $C_{20}H_{21}O_4N$, occurs in opium in small quantities (0.8 to 1.0 per cent.) and crystallises in prisms which melt at 147° . It is almost insoluble in water or alkalis.

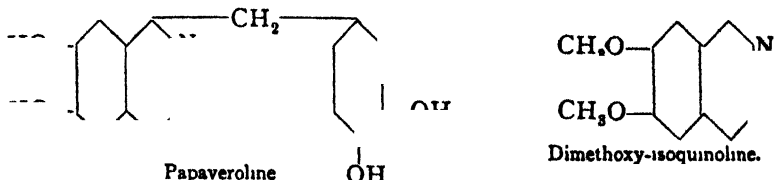


Papaverine

¹ See, for example, L. H. Briggs, H. T. Openshaw, and R. Robinson, *J.*, 1946, 953.

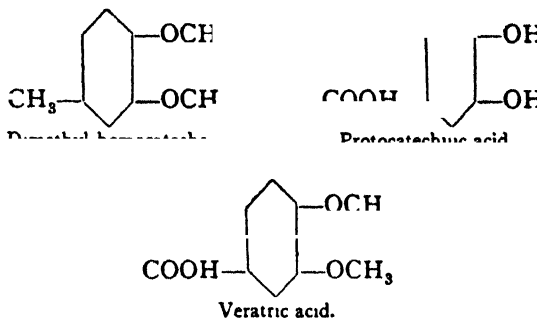
The constitution of papaverine was established by G. Goldschmiedt, from a long and detailed examination of the manner in which the compound is decomposed by halogen acids, potassium permanganate and fused alkali.

When the alkaloid is heated with hydriodic acid four molecules of methyl iodide are liberated and *papaveroline* is formed.



This reaction proves the presence of four methoxy groups in papaverine.

When fused with potash, papaverine is decomposed into *dimethoxy-isoquinoline* and a compound which does not contain nitrogen. The latter has been shown to be *dimethyl-homocatechol*, as it yields *protocatechuic acid* on more energetic treatment with potash. In addition, an appreciable quantity of *veratric acid* is always produced during the oxidation of the alkaloid. It will be observed that the side chains occupy the same positions in all these compounds.

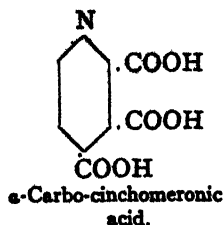


Constitution of Papaverine.—Papaverine can therefore be looked upon as a combination of dimethoxy-isoquinoline and dimethyl-homocatechol.



The manner in which these two components are joined together was determined by Goldschmiedt in the following way.

Papaverine contains four methoxy groups, two of which are contained in each of the above disruption products. Since the components cannot be united through the methoxy-groups, they must be joined through carbon atom of the benzene nucleus, or of the methyl group of dimethyl-homocatechol. The latter supposition is supported by the whole behavior of papaverine, especially the ease with which the component parts can be separated. Hence the alkaloid is a substituted *benzylisoquinoline*.

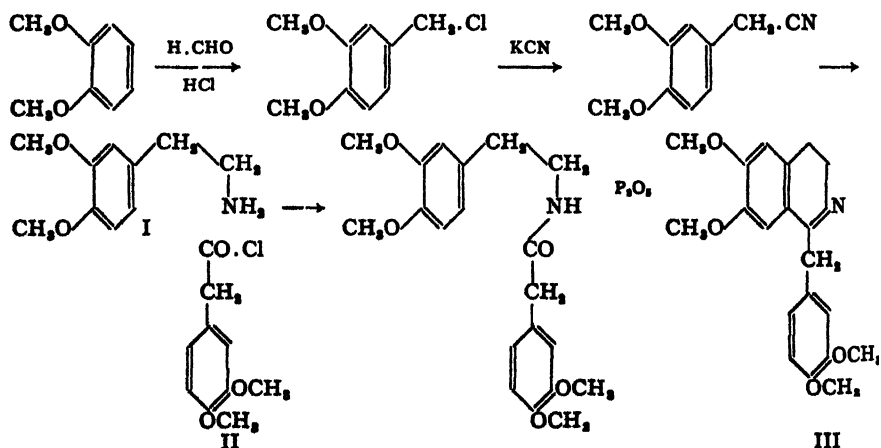


Finally, it was necessary to determine which carbon atom of the isoquinoline ring takes part in the union. This point was decided by the fact that *when papaverine is oxidised with potassium permanganate, α-carbo-cinchomeric-acid (2:3:4-pyridine tricarboxylic acid) is formed.*

Inspection of the formula of papaverine shows that it contains a methylene group in the 1-position situated between a phenyl and an isoquinoline nucleus. In consequence this methylene group is reactive and on oxidation yields the carbinol, *papaverinol*, or the ketone, *papa-veraldine*.



Synthesis of Papaverine.—The synthesis of papaverine was first accomplished by Pictet and Gams by a method which confirmed the accepted formula.¹ The synthesis has since been simplified and improved, the two main reactants homoveratrylamine and homoveratric acid both being obtained from veratrol.² Veratrol readily undergoes chloromethylation with formaldehyde and hydrochloric acid (see p. 462), and the resulting chloro-compound gives, with potassium cyanide 3:4-dimethoxybenzyl cyanide, from which homoveratrylamine (I) and homoveratric acid are prepared by catalytic reduction (Raney nickel) and hydrolysis respectively. Homoveratrylamine and the acid chloride (II)



react to give a product which, when heated with phosphorus pentoxide in xylene, gives dihydropapaverine (III). Papaverine is obtained by dehydrogenation with palladised asbestos at 200°.

A number of other syntheses of papaverine have been published in recent years.³

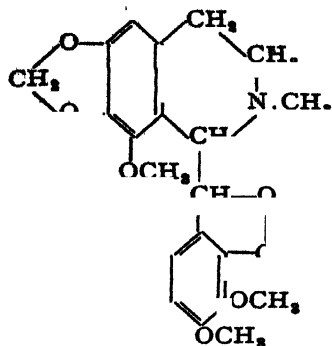
¹ A. Pictet and A. Gams, *Ber.*, 1909, 42, 2943.

² See A. E. Bide and Wilkinson, *J.S.C.I.*

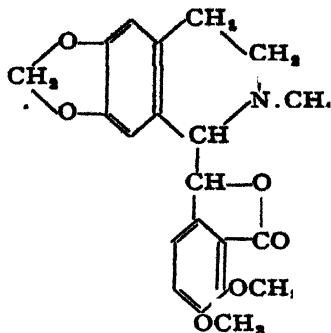
1945, 54, 84.

³ Buck, Haworth and Perkin, *J.*, 1924, 125, 2176. Rosenmund, Nothnagel and Riesenfeldt, *Ber.*, 1927, 60, 392. Buck, *J.A.C.S.*, 1930, 52, 3610. Mannich and Walther, *Arch. Pharm.*, 1927, 265, 1.

Narcotine and Hydrastine



Narcotine (methoxy-hydrastine)

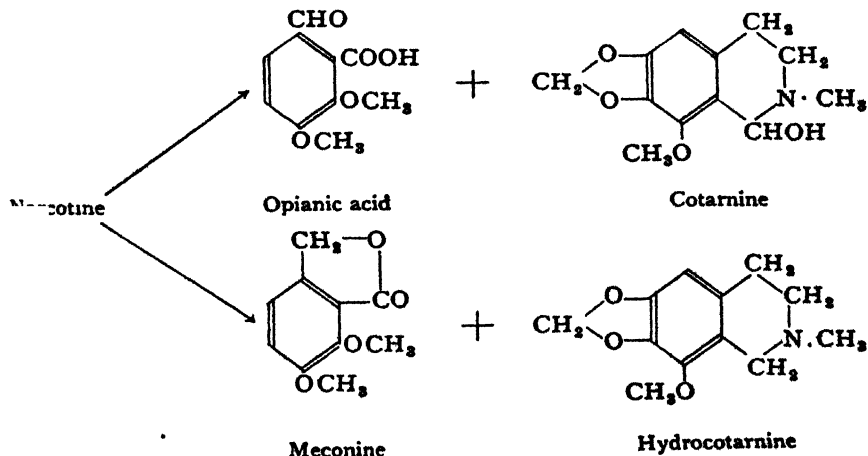


Hydrastine.

Narcotine, $C_{23}H_{23}O_7N$, is present as the free alkaloid in opium in quantities varying from 0.75 to 9 per cent. After the removal of morphine and codeine from opium by extraction with water, narcotine is obtained by treating the residue with warm ether. It crystallises in rhombic prisms, m.p. 176° , and is insoluble in cold alkali.

Narcotine is a tertiary base and, as it does not react with acetic anhydride, contains no free hydroxyl group. The presence of three methoxy groups is shown by heating the alkaloid with hydrochloric acid, when it yields three molecular proportions of methyl chloride together with *nornarcotine*, $C_{19}H_{14}O_4N(OH)_3$. The nitrogen is attached to a methyl group since narcotine is decomposed by potassium hydroxide at 220° with liberation of methylamine, dimethylamine and trimethylamine.

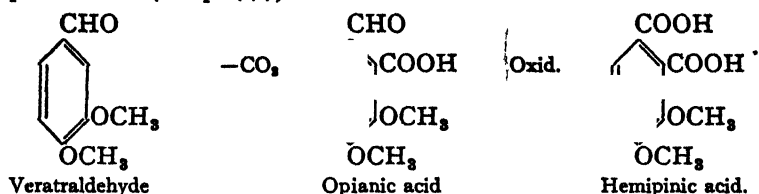
Constitution of Narcotine.—Our knowledge of the constitution of narcotine is largely due to the work of Roser.



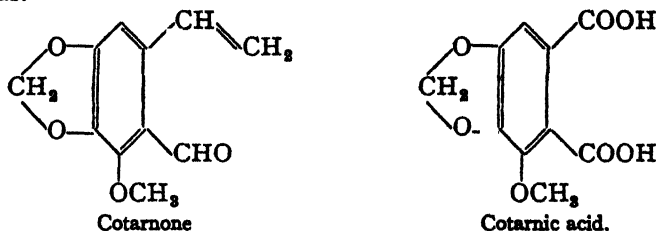
With oxidising agents such as nitric acid, platonic chloride, ferric chloride or lead peroxide, narcotine undergoes oxidation and hydrolysis to give *opianic acid* and *cotarnine*. Reducing agents such as zinc and hydrochloric acid convert narcotine into *meconine* and *hydrocotarnine*.

From these reactions it is evident that the molecule of narcotine consists essentially of two parts—a basic component corresponding to hydrocotarnine and a nitrogen-free fragment corresponding to opianic acid. To build up the formula of narcotine it is necessary first to determine the structure of the individual parts.

The structure of opianic acid follows from its decarboxylation to veratraldehyde (methylvanillin) and its oxidation to hemipinic acid. Meconine has been shown to be the lactone of the alcohol corresponding to opianic acid (see p. 777).



Cotarnine was shown by several reactions to be an isoquinoline derivative and further insight into its structure was obtained by synthesis (p. 779) and by methylation followed by decomposition with alkali when trimethylamine and the unsaturated aldehyde, *cotarnone*, were obtained. The aldehyde on oxidation gave *cotarnic acid*. The structure of these products was settled by the synthesis of cotarnic acid by Perkin, Robinson and Thomas.



On reduction cotarnine gives hydrocotarnine.

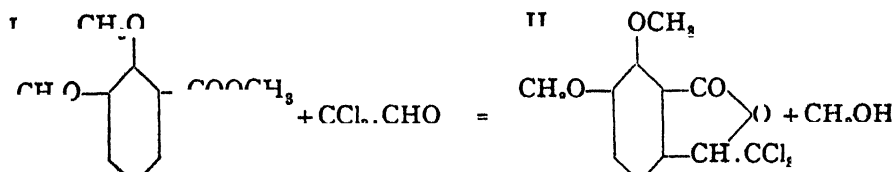
The constitution of the decomposition products opianic acid and meconine on the one hand, and cotarnine and hydrocotarnine on the other, is therefore clear. The only point to be decided is how the two component parts are linked together to form the alkaloid molecule.

In narcotine, $\text{C}_{22}\text{H}_{23}\text{NO}_7$, the hydro-cotarnine group cannot be united with opianic acid or meconine through one of the seven oxygen atoms, since five of these are already joined to alkyl groups (three to methyl and two to methylene) and the other two are both present in a lactone ring. Further, the valencies of the nitrogen atom are fully satisfied by the demands of the isoquinoline ring and the methyl group. The two

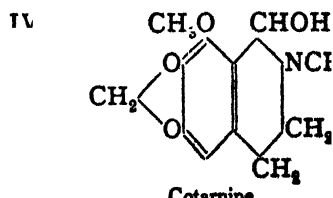
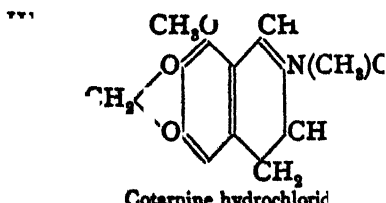
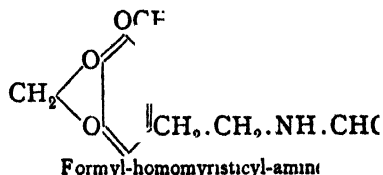
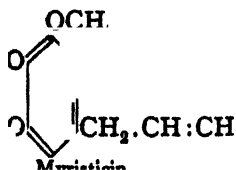
components must therefore be connected through carbon atoms. There is no doubt that it is these carbon atoms which take up oxygen during the oxidation of the alkaloid and appear as aldehyde groups in opianic acid and cotarnine, since no aldehyde group is present in narcotine itself. For these reasons narcotine is given the constitution quoted on p. 777.

Synthesis of Narcotine.—Perkin and Robinson showed that when meconine and cotarnine are boiled in alcoholic solution with potassium carbonate a compound is produced which is identical with the racemic alkaloid *gnoscopine*. By resolving this into its active components (+)- and (−)-narcotine were obtained, the (−)- variety being identical with the natural alkaloid.

Synthesis of Meconine.—Guaiacol carboxylic acid, on methylation, was converted into the methyl ester of 2 : 3-dimethoxy-benzoic acid, I. The latter was condensed with chloral to give 5 : 6-dimethoxy-trichloromethyl phthalide, II, which was then hydrolysed to the corresponding phthalide carboxylic acid. The acid, on being heated, decomposed into carbon dioxide and meconine.

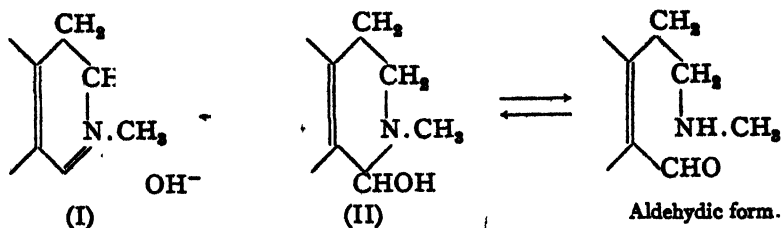


Synthesis of Cotarnine.—This base was synthesised by Salway, and later by Decker and Becker, from myristicin, a constituent of oil of parsley and oil of nutmeg. An intermediate product in the later synthesis was formyl-homomyristicyl-amine. (Compare the preparation of hydnastinine from safral.)



In aqueous or ethanolic solution cotarnine and its hydrochlorid have similar ultra-violet spectra, and on this and other evidence it is concluded that in such solutions cotarnine exists in the ammonium

form¹ (I). Addition of alkali, however, changes the ammonium form into a carbinol form (II), which is a weak base and is comparatively water-insoluble. This form in turn may be in equilibrium with an aldehydic form. The chemical and physical properties of cotarnine in solution may be accounted for in terms of a mobile equilibrium between the three forms.



The carbinol form is an example of a *pseudo-base*, a term coined by Hantzsch to describe weak bases obtained by the action of alkali on certain quaternary ammonium salts.

The equilibrium between II and the aldehydic form is an example of *ring-chain tautomerism*.

Hydrastine (see formula on p. 777) occurs in the root of *Hydrastis canadensis* L., a plant belonging to the Ranunculaceæ and indigenous to North America.

The structure of hydrastine, which was established by the work of Freund and E. Schmidt, is very similar to that of narcotine.

When hydrastine is oxidised with potassium permanganate in acid solution, opianic acid is formed.

On oxidation with dilute nitric acid at 50° to 60°, however, hydrastine yields, in addition to opianic acid, a basic compound of the formula $C_{11}H_{13}NO_3$, known as *hydrastinine*.



The difference of CH_2O between the molecules of cotarnine and hydrastinine, the basic decomposition products of narcotine and hydrastine respectively, indicates that cotarnine is a methoxy-hydrastinine. Narcotine must therefore be a methoxy-hydrastine with the methoxyl group attached to the basic part of the molecule. This conclusion was confirmed by the determination of the methoxyl group by Zeisel's method.

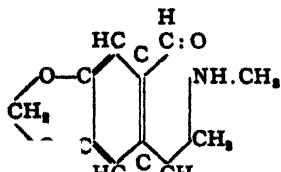
Hydrastinine is of the greatest importance in connection with the constitution of hydrastine. Its structure has been ascertained both by degradation and synthesis.

Synthesis of Hydrastinine

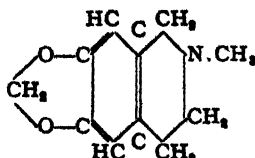
Hydrastinine (V) is a derivative of piperonal, containing a basic side chain in the ortho-position to the aldehyde group. When it is reduced with zinc and hydrochloric

¹ Dobbie, Lauder, and Tinkler, *J.*, 1903, 83, 598. B. Skinner, *J.*, 1950, 823.

acid, ring formation takes place with loss of oxygen and production of hydro-hydrastinine (VI). This compound is an isoquinoline derivative and formed an intermediate product in the first synthesis of hydrastinine to be effected.



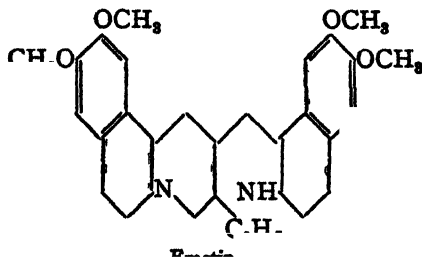
VI



Emetine and Cephaleine

Ipecacuanha has long been used medicinally as an emetic and purgative and also more recently in cases of amoebic dysentery. Pelletier in 1817 identified its most important active principle as the base **emetine**. In addition, ipecacuanha contains **cephaleine**, *psychotrine*, *o-methyl-psychotrine* and *emetamine*, all of which stand in close relationship to one another. Emetine and cephaleine have similar constitutions. Emetine is an O-methyl-cephaleine.

Emetine contains two 6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydroisoquinoline nuclei and the formula suggested by Robinson and Dewar¹ seems to be in harmony with the experimental evidence. One feature of this formula is the presence of an ethyl group—a group found only rarely in naturally occurring compounds.



Cephaleine possesses a similar constitution to emetine, but has a phenolic hydroxyl in place of a methoxyl group.

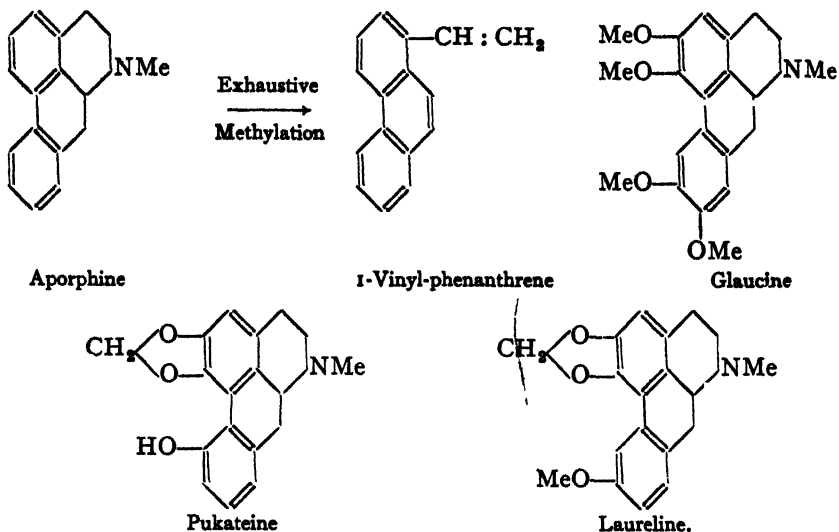
VII.—ALKALOIDS OF THE PHENANTHRENE GROUP

Aporphine Group

A number of the *Corydalis* alkaloids, including glaucine, bulbo-capnine and corytuberine are derivatives of aporphine, a base containing a condensed phenanthrene-pyridine structure. Glaucine and aporphine were synthesised by Gadamer; they are represented by the following abbreviated formulæ, in which the normal benzenoid nuclei are to be distinguished from the hydrogenated rings. (Me = methyl group.)

¹ R. Robinson, *Nature*, 1948, 162, 524. M-M. Janot, *Bull. Soc.*, 1949, 185.

Barger and his co-workers have established further examples of this type in laurotetanine (from various Lauraceæ) and in pukateine and laureline (from the bark of the Pukatea, *Laurelia Novæ Zealandiæ*).



From their general properties and behaviour on oxidation the last two compounds have been assigned the above constitutions. In physiological action they resemble morphine.

When submitted to exhaustive methylation aporphine yields 1-vinyl-phenanthrene. The methoxyl derivatives under similar treatment are converted into the corresponding 1-vinyl-methoxy-phenanthrenes.

Morphine Alkaloids¹

A comparison of the three alkaloids morphine, codeine, and thebaine suggests that they are closely related to one another. This is supported by the occurrence of the three bases in opium; by the fact that they are derivatives of phenanthrene; and by experimental investigations such as those described below.



For these reasons it is convenient to discuss morphine, codeine, and thebaine together, but owing to their greater practical importance, morphine and codeine will be treated in more detail.

Morphine is the chief basic constituent of opium, in which it is present in quantities varying from 3 to 23 per cent. It was the first alkaloid to be isolated from a plant source, and its discovery by the apothecary

¹ K. W. Bentley, *The Chemistry of the Morphine Alkaloids* (Oxford University Press, 1954).

Sertürner, in 1806, has been of great value to pharmacology and the development of organic chemistry. Its composition was shown by Laurent to correspond to the formula $C_{17}H_{19}NO_3 + H_2O$.

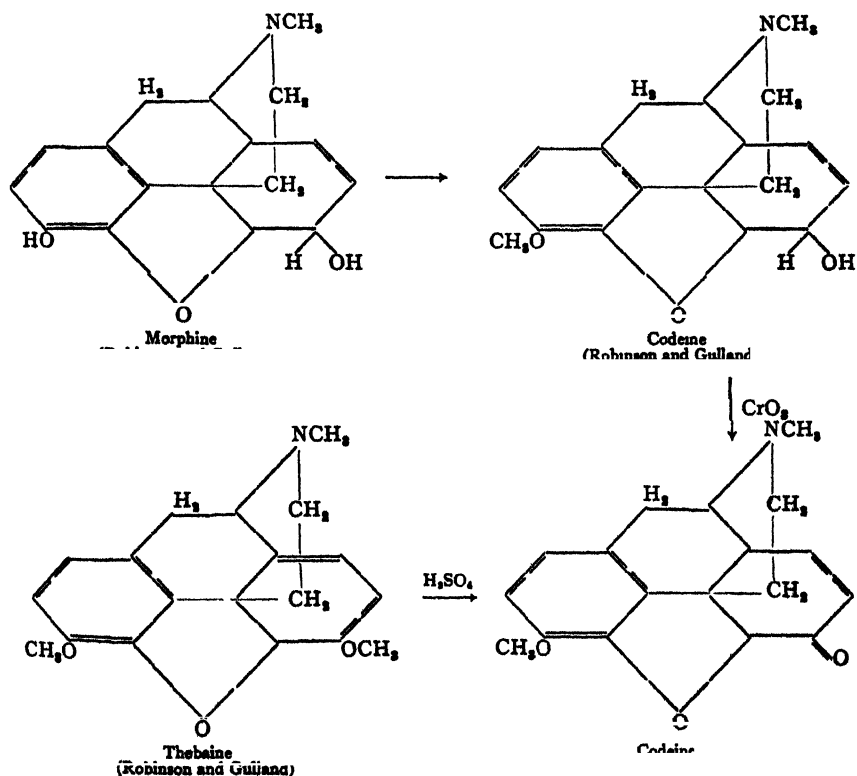
Morphine, m.p. 254° , has a bitter taste and is laevorotatory.

Codeine also occurs in opium, but in smaller quantities (0.3 to 2 per cent.) than morphine. From this source it was isolated by Robiquet in 1832. Gerhardt proved the formula of codeine to be $C_{18}H_{21}NO_3 + H_2O$, from which it was concluded to be a homologue of morphine. It is generally prepared from the latter compound.

Codeine, m.p. 155° , is laevorotatory, very poisonous and possesses a somewhat bitter taste. Like morphine it is a narcotic. Codeine and similarly constituted compounds are of greater medicinal value than morphine, on account of their sedative action and the fact that they reduce irritation of the air passages; hence they exert a favourable influence on respiration. Codeine is therefore a valuable specific in the treatment of coughs.

Thebaine, m.p. 196° , is present in opium.

Structure of Morphine, Codeine and Thebaine

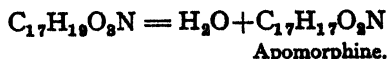


The above chart gives the formulæ of Robinson and Gulland now generally accepted for morphine, codeine, and thebaine and shows

how they are related to one another. Codeine is the phenolic methyl ether of morphine, while thebaine is the methyl ether of the enolic form of *codeinone*, the ketone obtained by oxidation of codeine.

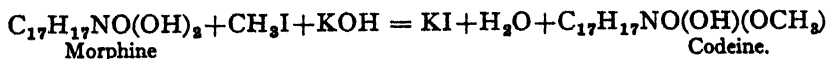
The numerous and difficult investigations of these alkaloids have been directed to showing the presence of a phenanthrene nucleus, and determining the function and position of the three oxygen atoms, nitrogen atom, and the $-\text{CH}_2\cdot\text{CH}_2\cdot\text{N}(\text{CH}_3)-$ chain.

Dehydration of morphine with sulphuric acid, phosphoric acid, etc., gives *apomorphine* by elimination of water according to the equation:



The appended formula of apomorphine was derived from degradation experiments and confirmed by synthesis, and indicates that morphine is a phenanthrene derivative with oxygen atoms in positions 5 and 6. The presence of the phenanthrene nucleus was shown by the distillation of morphine with zinc dust when phenanthrene was obtained.

The three oxygen atoms of morphine possess different functions. One is present as a *phenolic hydroxyl group*, which endows the alkaloid with certain acidic properties. The alkaloid can therefore be acetylated, etc., and methylation gives codeine.

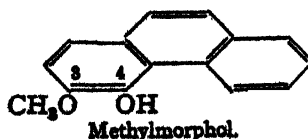
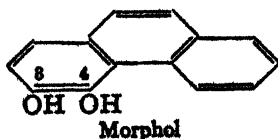


Codeine is therefore a methyl ether of morphine.

The second oxygen atom in morphine and codeine occurs as a *secondary* alcoholic group $>\text{CHOH}$, since Hesse showed that codeine on oxidation yields the ketone *codeinone*.

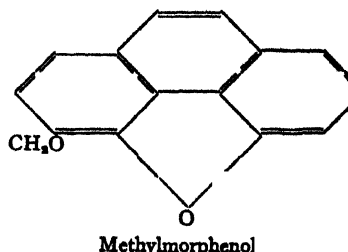
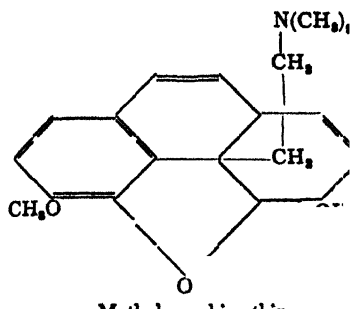
The third oxygen atom is very inert and was shown by Vongerichten and others to be present in an ether linkage. The information on this and other points came from degradation experiments some of which may be mentioned.

Morphine and its derivatives yield oxygenated phenanthrene derivatives on treatment with acetic anhydride. Thus morphine methiodide gives the diacetyl derivative of morphol (p. 613), identified as 3:4-dihydroxyphenanthrene, while α -methylmorphimethine (see below), obtained from codeine, gives methylmorphol (p. 613), 3-methoxy-4-hydroxyphenanthrene (as the acetyl derivative), dimethylamine, and acetoxyethyl-dimethylamine, $\text{CH}_3\text{CO}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{N}(\text{CH}_3)_2$.

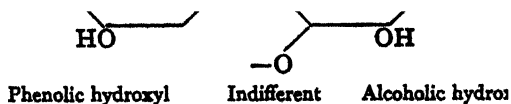


The methoxy group in codeine and the phenolic hydroxyl group in morphine each occupies the 3-position in the phenanthrene nucleus.

The hydroxyl group in position 4 in the above decomposition products was shown to correspond to the indifferent oxygen atom in the alkaloids by studies in the decomposition of the important compound α -methylmorphimethine, which is obtained from codeine methiodide by treatment with alkali. One carbon-nitrogen bond is broken and water is eliminated to introduce a double bond at C_9-C_{10} . When α -methylmethimorphine is exhaustively methylated and the quaternary base heated, an atypical decomposition results, methylmorphenol being obtained together with trimethylamine, ethylene, and water



Hence the position of the ether linkage is established. Finally Knor obtained 3-methoxy-4:6-dihydroxyphenanthrene as one of the decomposition products of codeinone and concluded that the alcoholic hydroxy group is attached to position 6. Hence the alkaloids morphine and codeine are derivatives of 3:4:6-trihydroxyphenanthrene, and other investigations showed that thebaine is also derived from this compound. The functions of the three oxygen atoms in morphine may therefore be

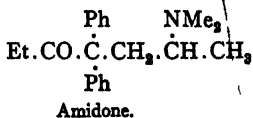


Of the 17 carbon atoms in the morphine molecule 14 must belong to a phenanthrene nucleus. It thus remains to account for the other three carbon atoms and the nitrogen atom. Morphine unites directly with one molecule of methyl iodide to give a methiodide. This is in agreement with its behaviour on exhaustive methylation which showed that the nitrogen is contained in a ring, is attached to three carbon atoms, and is therefore tertiary. Important deductions were made from the

nitrogenous fragments obtained in some of the decompositions already outlined, namely, dimethylamine, trimethylamine, and derivatives of hydroxyethyl-dimethylamine, $\text{HO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{N}(\text{CH}_3)_2$. A vast amount of research was required before the $-\text{C} \cdot \text{C} \cdot \text{N}(\text{CH}_3)_2-$ fragment could be built into the molecule. It must suffice to say that the most obvious solution, namely, a ring structure as in apomorphine is ruled out and that the formulæ of Robinson and Gulland account satisfactorily for all the known reactions of the three alkaloids. This has been substantiated by the synthesis of morphine.¹

Apomorphine (p. 784) is quite different physiologically from morphine; it is not a narcotic but an expectorant and emetic.

Morphine Substitutes.—Various attempts have been made to find substances as effective as morphine without its disadvantages. One of the most promising is (\pm) -2-dimethylamino-4:4-diphenylheptane-5-one which is sold under various names such as *Amidone* or *Physeptum*.



It is reported to have analgesic properties twice as potent as those of morphine, not to lose its effect on repetition, nor depress respiration.

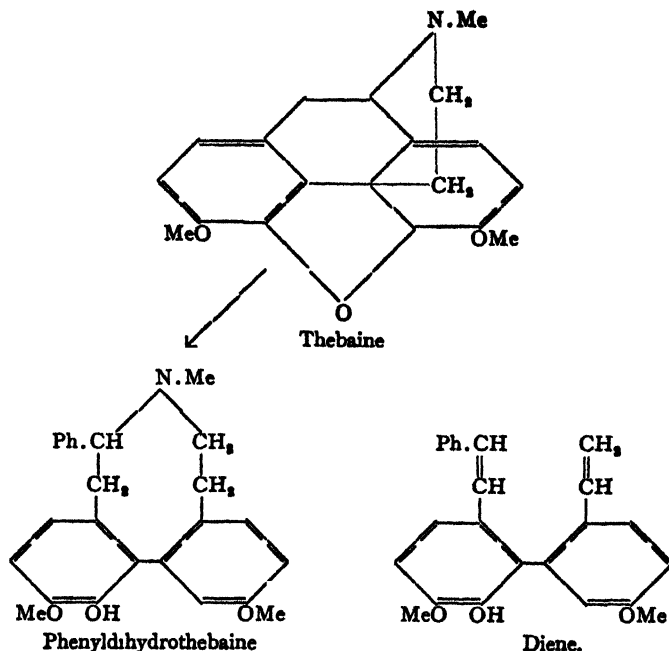
Phenyldihydrothebaine

No description of the morphine alkaloids would be complete without including what Robinson has described as "one of the most extraordinary changes yet encountered in the whole domain of chemistry." Freund in 1905 discovered that phenylmagnesium bromide reacted with thebaine to give *phenyldihydrothebaine*, and this reaction has been thoroughly studied by Lyndon Small. It has been left, however, to Robinson² to interpret by a brilliant analysis the somewhat puzzling experimental data.

Thebaine differs considerably in its properties from phenyldihydrothebaine. It readily undergoes catalytic hydrogenation while phenyldihydrothebaine does not. Thebaine is hydrolysed to an enol methyl ether, but phenyldihydrothebaine is indifferent to hot hydrochloric acid. Both contain two methoxy groups, but phenyldihydrothebaine contains in addition a hydroxy group and with hydrobromic acid is hydrolysed to a trihydroxy compound, which with diazomethane yields a trimethoxy product (*phenyldihydrothebaine methyl ether*). These facts can be explained if phenyldihydrothebaine contains *two* benzene rings. This means that thebaine has a benzene ring and a partially reduced ring and phenyldihydrothebaine a diphenyl nucleus. This difference is included

¹ M. Gates and G. Tschudi, *J.A.C.S.*, 1952, 74, 1109. ² K. W. Bentley and R. Robinson *J.*, 1952, 947.

in Robinson's picture of the thebaine-phenyldihydrothebaine change as shown in the first stage of the following equation.



This picture of a remarkable molecular rearrangement to give the above nine-membered ring structure for phenyldihydrothebaine was reached by a novel and ingenious line of argument. Phenyldihydrothebaine is optically active and undergoes the Hofmann degradation to give a diene which is also optically active. Now phenyldihydrothebaine has 25 carbon atoms, two of which are present in methoxy groups and one is lost with the nitrogen during the conversion to the diene. The skeleton structure of the latter must therefore contain 22 carbon atoms, 18 of which form three benzene rings. The two double bonds accordingly must be shared by four carbon atoms, and hence there is no asymmetric carbon atom in the molecule. It follows that the optical activity of the diene must be due to molecular dissymmetry of the diphenyl type (p. 38), planarity being prevented by the two ethylenic groups. The formula for the diene given above has been experimentally confirmed and lends plausibility to the Robinson formula for phenyldihydrothebaine.

Another feature of great interest emerges. The experiments of Lyndon Small showed clearly that there are two asymmetric elements in the phenyldihydrothebaine molecule, and the conclusion seems unavoidable that one of these must be ascribed to an asymmetric carbon atom and the other to molecular dissymmetry similar to that in the above diene molecule. Models show that the proposed structure is satisfactory, the flexible nine-membered ring permitting the phenyl nuclei to be inclined at any angle to one another without strain. Confirmation of

this comes from absorption spectra measurements which on account of the nuclei being non-planar do not show the typical diphenyl band (see p. 88).

It follows that the generalisation on p. 29 should be altered to read: a compound of unsymmetrical structure containing *n* asymmetric centres can exist in 2^n optically active isomerides.

ALKALOIDS OF THE MEADOW SAFFRON

To this group belong colchicine, $C_{21}H_{23}NO_6 + \frac{1}{2}H_2O$, and colchicine, $C_{22}H_{25}NO_6$. Colchicine melts at 155° and is very poisonous. It is employed medicinally in cases of rheumatism and gout. Structurally colchicine is of great interest since of the three rings it contains one is benzenoid; one is a seven-membered ring; and the third has the structure of a tropolone methyl ether.¹

Colchicine has a remarkable influence on the growth and heredity of plants when injected into the buds or used as a bath. This treatment leads to the appearance of large numbers of new varieties, the characteristics of which are hereditary. Astonishing changes have thus been effected in numerous species.

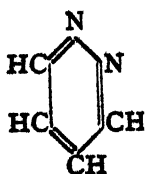
VIII Azines

Under the heading of *azines* are grouped various classes of compounds containing a six-membered ring built up of carbon and two or more atoms of nitrogen, or of carbon and nitrogen together with oxygen or sulphur. Compounds of this type containing oxygen are termed *oxazines*; those containing sulphur are known as *thiasines*.

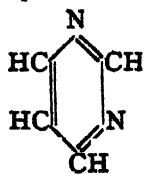
The azines are usually named in accordance with the number of nitrogen atoms in the ring, *e.g.* diazines, triazines, tetrazines, etc. These six-membered rings may be compared with the five-membered azole rings previously described. Belonging to this group are important classes of dye-stuffs.

I.—DIAZINES

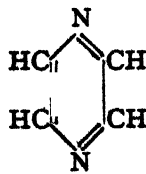
The simplest azines, containing a ring composed of four carbon atoms and two nitrogen atoms, will be taken first. Three series of diazines, derived from the following compounds, are known:—



Orthodiazine,
Pyridazine



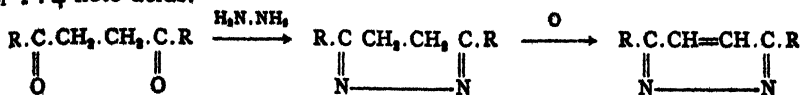
Metadiazine,
Pyrimidine



Paradiazine,
Pyrasine.

¹ J. W. Cook and J. D. Loudon, *Quart. Rev.*, 1951, 5, 104.

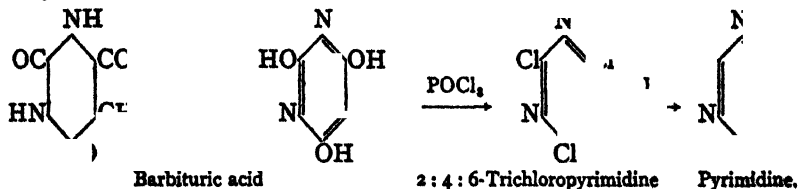
Pyridazines can often be prepared by the oxidation of their dihydro-derivatives obtained by the condensation of hydrazines with 1 : 4-diketones or 1 : 4-keto-acids.



The parent substance, *pyridazine*, results from the action of hydrazine hydrate on maleic dialdehyde. It is a colourless liquid, b.p. 208°. The base has an odour resembling that of pyridine.

The best-known azines are the **pyrimidines**,¹ the nucleus of which is contained in many substances of physiological and therapeutic importance such as vitamin B₂, sulphadiazine, barbiturates, purines, nucleic acids, etc. They are generally prepared by the condensation of diamino or amino-imino compounds such as urea or thiourea with the esters or nitriles of dicarboxylic acids—diethyl malonate, ethyl cyanacetate, etc. The preparation of barbituric acid (p. 359), veronal (p. 360), and the pyrimidine half of vitamin B₁ (p. 843) are typical.

Another method of preparation is based on the tautomeric behaviour of many pyrimidines. These may exist in keto or enolic forms and the latter react with phosphorus oxychloride to form chloro derivatives, which on reduction yield pyrimidines. Pyrimidine, the parent compound of this group, is prepared from barbituric acid in this way; but is best prepared by the catalytic reduction in the presence of magnesium oxide of 2 : 4-dichloropyrimidine.²

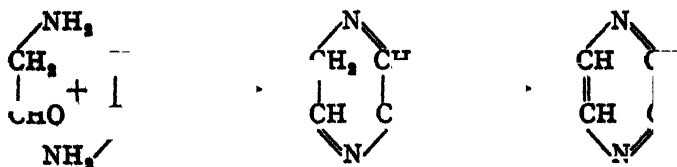


It is a crystalline compound, m.p. 22°, b.p. 124°, which dissolves readily in water.

The hexagonal structure of the pyrimidines has been proved by X-ray analysis.

Other derivatives of pyrimidine which are present in nucleic acids are **uracil**, **thymine**, and **cytosine** (see p. 360).

The **pyrazines**³ are prepared by the condensation of two molecules of α -amino-aldehydes or α -aminoketones. Two molecules of water are



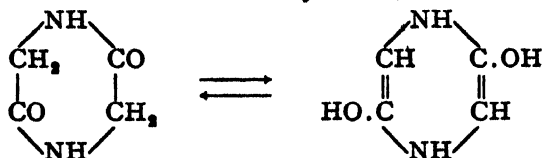
¹ See "Some Aspects of Pyrimidine and Purine Chemistry" by B. Lythgoe, *Quarterly Reviews*, 1949, 3, 181. ² N. Whittaker, *J.*, 1953, 1646. ³ G. T. Newbold and F. S. Spring,

eliminated and the intermediate dihydropyrazine compound is oxidised by atmospheric oxygen, *e.g.*

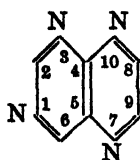
The pyrazine nucleus is not so stable as that of pyridine. For example, pyrazine carboxylic acids are obtained by oxidation of the homologues but in poor yield, probably due to oxidation of the nucleus.

Pyrazine itself is produced by the condensation of amino-acetaldehyde or amino-acetal. It melts at 55°, boils at 116°, and has an odour of heliotrope. The properties of pyrazine closely resemble those of the lower homologues. It is a weak monoacid base, neutral to litmus, hygroscopic, and forms derivatives such as a monomethiodide, picrate, etc. Its reduction product, *piperasine*, which is a strong diacid base, has already been described on p. 264.

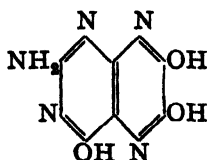
Among other derivatives of piperazine are the 2 : 5-*diketo-piperazines*, described on p. 247. These have been used in the synthesis of polypeptides. 2 : 5-Diketopiperazine is a tautomeric compound, which theoretically can exist in five different forms. Its reactions, however, point to the presence of two forms only—the diketo and the dihydroxy.



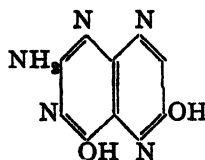
Pterins.¹—A number of pyrimidine compounds occur as pigments in butterfly wings and are called *pterins*. They are derivatives of *pteridine* (see formula), and are exemplified by the two naturally-occurring pterins, *leucopterin* and *xanthopterin*.



Pteridine



Leucopterin

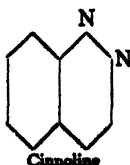


Xanthopterin

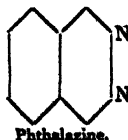
II.—BENZO-DIAZINES

The ring systems described under diazines may also occur in combination with benzene nuclei, thus giving rise to a number of new classes of compounds. These are termed mono-benzo-diazines or dibenzo-diazines, according as one or two benzene nuclei are condensed with the diazine ring.

From pyridazine are derived *cinnolines* and *phthalasines*.



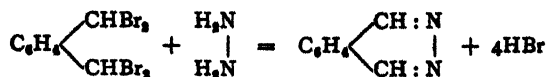
Cinnoline



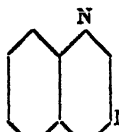
Phthalazine.

¹ J. C. E. Simpson, *Ann. Reports*, 1946, 43, 250.

Phthalazine is obtained by the action of hydrazine on ortho-derivatives of benzene which are brominated in the side chain.



Pyrimidines and pyrazines give rise respectively to quinazolines and quinoxalines.

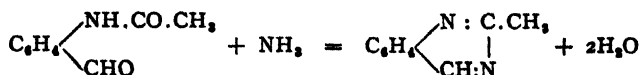


Quinazoline

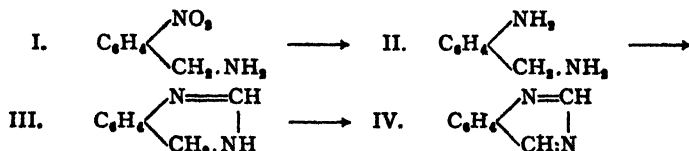


Quinoxaline.

Quinazolines are prepared by the action of ammonia on acyl derivatives of *o*-amino-benzaldehydes.



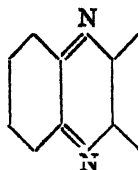
They are strong bases, which are readily reduced to their dihydro-compounds. *Quinazoline* itself is a solid, m.p. 48° and b.p. 243° . It is obtained from *o*-nitro-benzylamine (I), which is first reduced to *o*-amino-benzylamine (II). The latter is then treated with formic acid, and the dihydro-quinazoline (III) so obtained is oxidised to quinazoline (IV).



The preparation of **quinoxalines** by the condensation of *o*-diamines with 1:2-diketones has been mentioned on pp. 270 and 473. These are weakly basic compounds, which may be reduced to hydro-quinoxalines, but are stable towards oxidising agents.

In the dibenzo-diazine series the most interesting compounds are the **phenazines**. Several important classes of dye-stuffs, such as the eurhodines, indulines and safranines, belong to this group.

The simplest example is **Phenazine**, which crystallises in bright yellow needles, m.p. 171° . and is easily sublimed.



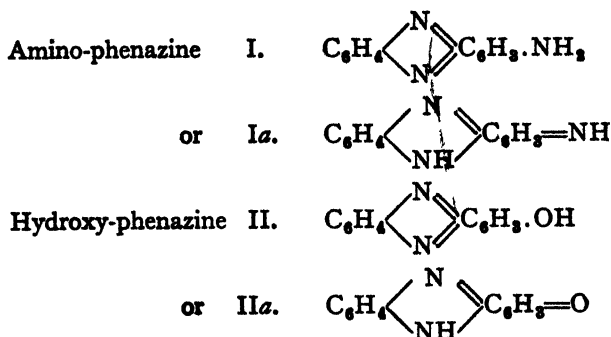
Phenazine may be synthesised by heating a mixture of catechol and *o*-phenylene diamine. In general, phenazines are formed by the action of *o*-diamines on *o*-quinones.



The majority of the phenazines are yellow, weakly basic compounds, which distil unchanged. Their colour is due to the presence of the

chromophore group . Simple azines, such as phenazine, are

not in themselves dye-stuffs, but they become so on the entrance of amino or hydroxyl groups into the molecule. Before proceeding further, it should be mentioned that, in addition to the usual formulæ of types I and II for the amino- and hydroxy-phenazines, the para-quinonoid formulæ Ia and IIa have certain advantages, although the basic properties of the amino-compounds and the phenolic properties of the hydroxyl compounds support I and II.



Careful consideration of all the facts has led to the conclusion that these compounds are probably tautomeric, each reacting in the two forms indicated.

Azine Dye-stuffs

The azine dye-stuffs may be divided into the following classes.

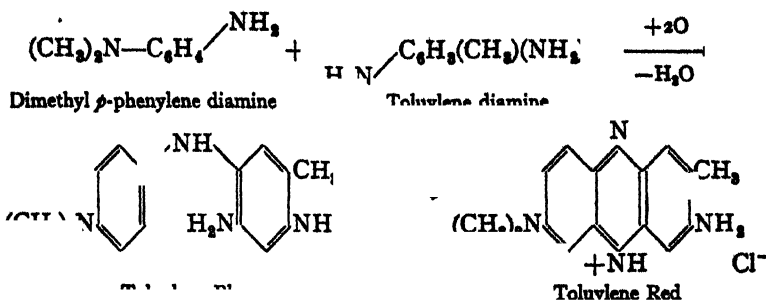
- (1) Eurhodines
- (2) Safranines
- (3) Aposafranines
- (4) Indulines

A few of the more important dyes belonging to each series are described in the following pages.

1. Eurhodines or Aminophenazines

Toluylene Red is a typical eurhodine which is formed by oxidising a mixture of *p*-aminodimethylaniline and *m*-toluylene diamine at the boiling-point. *Toluylene blue*, an indamine derivative, occurs as an intermediate product and is converted into toluylene red by elimination of hydrogen.

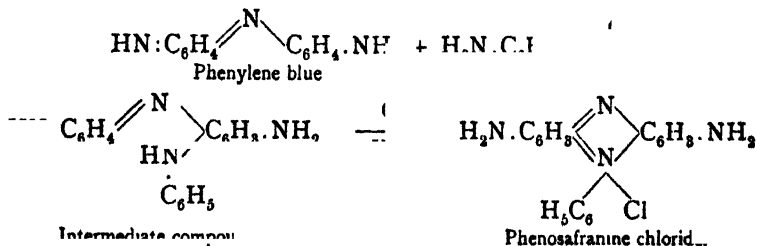
Toluylene red crystallises in orange-red needles, dyes silk and tannin-mordanted cotton a scarlet red, and is used commercially under the name "mordant red."



The simplest eurhodines are weakly basic dye-stuffs, giving monacid salts which dye silk a red colour. As, however, the salts are dissociated in water, this red colour is changed into the yellow of the base on washing.

2. Safranines

The safranines are among the oldest of the coal-tar dye-stuffs, since one of their number, Mauveine, was the first artificial dye-stuff to be manufactured. They are phenazonium salts with amino groups in positions 3 and 7, and a phenyl (or substituted phenyl) group on N₁₀ (see formulæ below). They are strongly basic crystalline compounds which

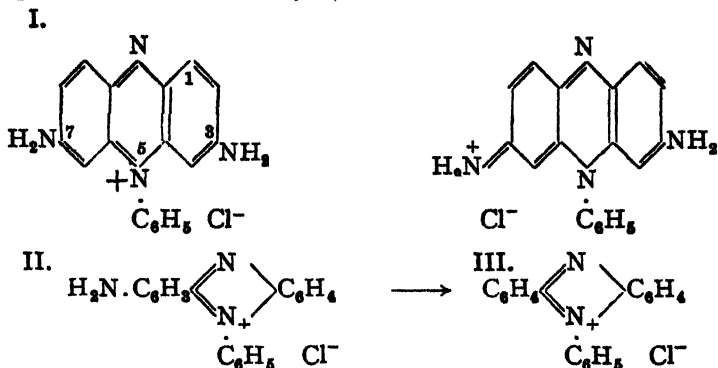


are readily soluble in water and dye yellowish red to violet colours. They may be prepared by the oxidation of a mixture of a *p*-diamino-diphenylamine, or of an indamine, with a primary monamine.

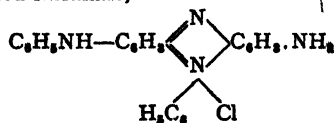
The safranines form three series of salts, monacid (red), diacid (blue) and triacid (green). Only the monacid salts are stable towards water, the others are decomposed by it. Animal fibres, as well as tannin-mordanted cotton, are dyed red by the safranines.

The constitution of the safranines was solved by the work of Nietzki and Kehrmann. Phenosafranin, the simplest member of the group, has been shown to be the phenyl-ammonium derivative of symmetrical diamino-phenazine. Its hydrochloride is represented as in formula I. When the diazonium compound of this base is heated with alcohol, one amino-group is eliminated and aposafranin (II) is formed. In a similar

manner the diazonium derivative from the latter may be converted into phenyl-phenazonium chloride (III).



Mauveine, the first aniline dye-stuff to be prepared industrially, is of great historical interest and may well be regarded as the beginning of the modern chemical industry. It was obtained by Perkin in 1856, by the oxidation of crude aniline, and consists of a mixture of phenylated safranin,

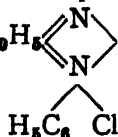


and its homologues.

3. Aposafranines

Aposafranin, which is formed by the elimination of one amino-group from phenosafranin (see p. 793), is a typical member of a comparatively large group of dyes. In this group are now included many compounds formerly classed as indulines, such as the rosindulines and iso-rosindulines, both of which contain a naphthalene nucleus. In the *rosindulines* the amino-group is present in the naphthalene nucleus, and in the *iso-rosindulines* in the benzene nucleus (O. Fischer and Hepp).

Rosinduline is prepared by heating benzene-azo- α -naphthylamine with aniline and alcohol under pressure, and also by other methods. Its hydrochloride, $\text{H}_2\text{N}-\text{C}_{10}\text{H}_7-\text{N}=\text{N}-\text{C}_6\text{H}_5$, is a red dye. The disulphonic



acid dyes a yellowish red shade.

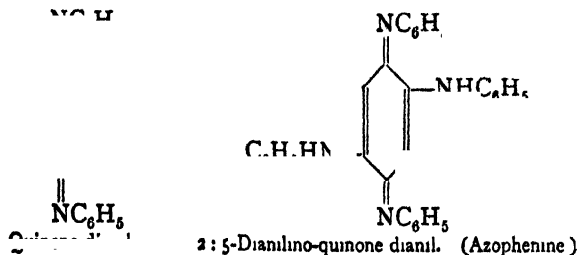
Phenyl-rosinduline, a derivative in which the amino-group of rosinduline is phenylated, is obtained by heating benzene-azo- α -naphthylamine with aniline and aniline hydrochloride. Its disulphonic acid is used commercially as a red dye-stuff for wool, under the name of **azocarmine**.

4. Indulines

The indulines, the first example of which was prepared in 1863 by Dale and Caro, give shades resembling those of indigo blue. They

occur as by-products in the "magenta melt," and are prepared by heating aminoazo-benzene with primary aromatic amines and their salts (induline melt).

The induline, **Indamine Blue**, is prepared by heating aminoazo-benzene with aniline hydrochloride (Dale and Caro, 1863). The inter-



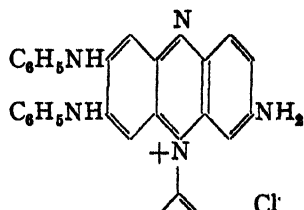
mediate compounds in this reaction have been shown to be quinone dianil and 2:5-dianilino-quinone dianil, or *azophenine*.

O. Fischer and Hepp proved that Indamine Blue has the annexed formula.

Some of the most important indulines were synthesised by Kehrman.

Induline gives reddish violet salts which are soluble in water, and are used directly on tannin-mordanted cotton.

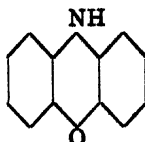
On heating the dye with aniline and aniline hydrochloride, more phenyl and amino-phenyl groups enter the molecule, with the formation of complex indulines. These are insoluble in water and are used either in alcoholic solution (spirit indulines), or in the form of their water-soluble sulphonic acids, for dyeing wool. Cotton may be dyed with the aid of *acetin*, a mixture of glyceryl esters of acetic acid, which acts as a solvent. For this purpose, induline is made into a paste with tannin and acetin, and printed on to the material. The acetin dissolves the dye and ensures the formation of the tannin lake. On subsequent treatment with steam the acetin is hydrolysed to glycerol and acetic acid and the lake is deposited on the fibres.



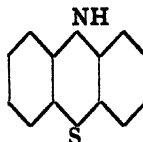
Aniline Black is a very valuable dye which is formed when aniline is oxidised by various reagents (such as sodium and potassium chlorates in presence of copper and vanadium compounds). It is always produced directly on the fibre and is widely employed in calico-printing and cotton-dyeing, but is not much used for wool. It is an amorphous, violet-black powder, which is insoluble in water and alcohol, is strongly basic and forms green, unstable salts with acids. The constitution of aniline black is not known with certainty on account of the complexity of the dye, but a plausible formula has been advanced by A. G. Green and Wolff (1913).

III.—OXAZINE (AZOXINE) AND THIAZINE (THIONINE) DYES

These compounds contain a nucleus built up of four carbon atoms, a nitrogen atom, and, according as they are derived from phenoxazine or phenothiazine, an atom of oxygen or sulphur.



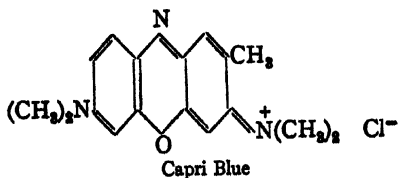
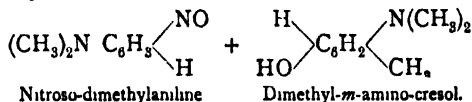
Phenoxazine

Phenothiazine,
Thio-diphenylamine.

The amino and hydroxy derivatives of these parent substances are leuco-compounds, which on oxidation give the corresponding dyes. *Phenoxazine* crystallises in plates, m.p. 148°, and is prepared by fusing *o*-amino-phenol with catechol.

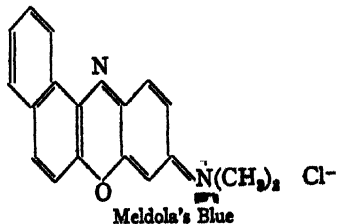
The phenoxazine dye-stuffs are prepared by the condensation of nitroso-dimethylaniline, nitroso-phenols, or quinone dichloro-imines with tertiary amino-phenols or polyhydric phenols.

In this way the dye **Capri Blue** is obtained by the interaction of nitroso-dimethylaniline and dimethyl-*m*-amino-cresol.



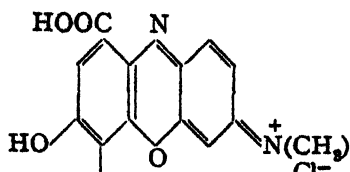
By replacing the methyl groups by other alkyl radicals a series of Capri Blues can be obtained. They possess the rather unusual property of dyeing acetate silk.

Meldola's Blue is prepared by the action of excess *p*-nitrosodimethylaniline on β -naphthol. The dye leuco-compound is first formed and is oxidised by the excess nitroso-compound to the dye.



It dyes tannin-mordanted cotton a violet blue shade but is not fast to alkali.

Gallocyanin is formed by the action of nitroso-dimethylaniline on gallic acid. It is a carboxylic acid of the annexed formula.

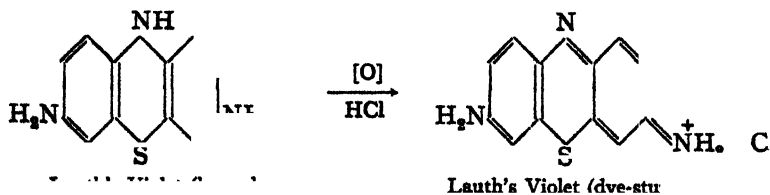


Gallocyanin is a mordant dye, which gives a fine blue-violet lake with chromium oxide. It is largely used in calico printing.

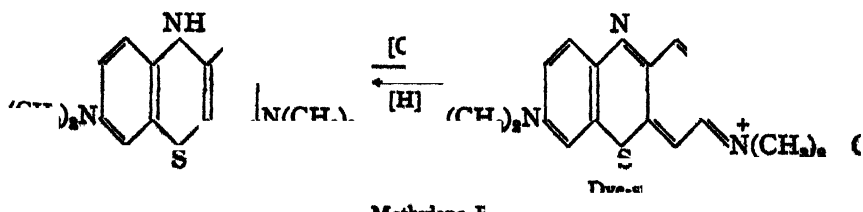
On heating gallocyanin with aniline the carboxyl group is replaced by the group $\text{—NHC}_6\text{H}_5$. When the latter is sulphonated by heating the compound with concentrated sulphuric acid, a sulphonic acid is obtained which is used commercially under the name of *Delphine blue*.

Phenthiazine (see p. 796), is also the parent compound of a number of dye-stuffs and is an excellent anthelmintic (worm destroyer) and insecticide. It melts at 185° , and is prepared in an analogous manner to phenoxazine by heating diphenylamine with sulphur or sulphur chloride. The introduction of amino-groups into phenthiazine lead to the formation of leuco-compounds, which on oxidation yield dyes.

The first thiazine dye was prepared by Lauth by oxidising *p*-phenylenediamine hydrochloride in a solution containing hydrogen sulphide. The **Lauth's Violet** so obtained has the formula given below, since it is also obtained from the leuco-base whose structure has been established.



One of the best known thiazine dyes is **Methylene Blue**, which obtained by a somewhat complex process in which *p*-aminodimethylaniline and dimethylaniline are oxidised in the presence of sodium thiosulphate and zinc chloride. Its constitution follows from the methylation of the leuco-base of Lauth's Violet which yields the leuco-base

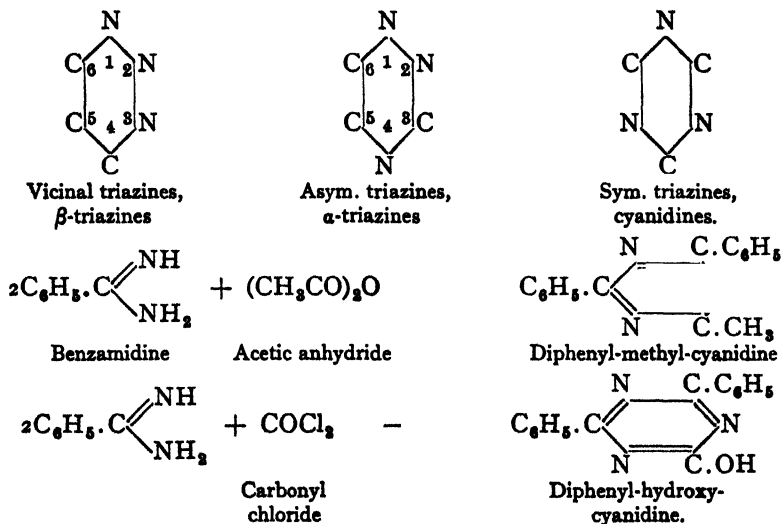


Methylene Blue. Oxidation of the leuco-base gives the dye and the regeneration of the leuco-base is effected by reduction.

The dye is precipitated from aqueous solution by the addition of zinc chloride and common salt, and is placed on the market in the form of its zinc chloride double salt. The latter is very soluble in water. It does not dye wool readily but is used for silk and tannin-mordanted cotton, the colour being very fast to light. It is the most important of all the blue basic dyes, and is widely used in calico-printing and cotton-dyeing. Koch showed that Methylene Blue stains the tubercle and cholera bacilli and the dye is used as a microscope stain.

IV.—TRIAZINES

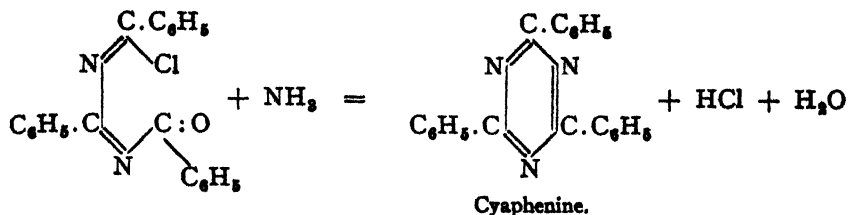
Three different six-membered rings composed of three nitrogen and three carbon atoms are theoretically possible. Derivatives of all three types are known, but only those of the sym. triazines are of importance: a large number of compounds belong to this class and some of these have already been mentioned (cyanuric acid, cyamelide and melamine, p. 348 *et seq.*).



A general method of preparing the derivatives of **symmetrical triazine**, **cyanidines**, is by the action of acid anhydrides, or of carbonyl chloride, on aromatic amidines.

Many cyanidines may be obtained by the action of aluminium chloride on a mixture of benzonitrile and benzoyl chloride or a fatty acid chloride. In the reaction between benzonitrile and benzoyl chloride it is advantageous to add ammonium chloride to the mixture, when cyaphenine or triphenyl cyanidine is produced in moderately good yield. This is one of the earliest known cyanidines. The reaction is probably due to the initial formation

of a condensation product of benzonitrile and benzoyl chloride, which then interacts with ammonia in the following manner :



Cyaphenine crystallises in colourless needles which melt at 233° , and readily sublime. Its constitution follows from its formation by the action of sodium on a mixture of cyanuric chloride and bromo-benzene. It has no basic properties, and is decomposed by nascent hydrogen into ammonia and lophine (2 : 4 : 5-triphenyl-glyoxaline).

IX

Proteins¹

Proteins may be defined as naturally occurring substances of high molecular weight, which are solely or largely composed of α -amino-acids united by an amide type of linkage. They are of great biological interest and significance since they include some of the most important constituents of the living cell. So intimately are they bound up with the life processes and so great is their specificity that each type of organism and each kind of cell possesses its own characteristic proteins. Proteins in fact are essential constituents of living matter, and their importance has been increased by modern research which has demonstrated that enzymes and viruses are proteins.

A certain quantity of the protein in living organisms is continually being used up in vital processes (*e.g.* gland secretions) and it is necessary for the loss to be replaced. For this purpose plants utilise inorganic nitrates as their main source of nitrogen. The animal body is incapable of building up all the requisite constituents of protein molecules from nitrates and non-nitrogenous organic substances, such as carbohydrates and fats, and consequently makes use of ingested protein to replace the loss. Protein is therefore an essential constituent of animal diet. At one time it was considered that proteins were in themselves sufficient to maintain life, and that the most satisfactory and economical diet was one containing the highest possible proportion of protein. This was

¹ Two good introductions to the subject are : M. V. Tracey, *Proteins and Life* (The Pilot Press, 1950) and F. Haurowitz, *Chemistry and Biology of Proteins* (Academic Press, New York, 1950). More extensive or specialised reviews are : Carl L. A. Schmidt, *Chemistry of the Amino-acids and Proteins*. E. J. Cohn and J. T. Edsall, *Proteins, Amino-acids, and Peptides as Ions and Dipolar Ions*. M. V. Tracey, *Ann. Reports*, 1949, 46, 211. R. L. M. Synge, *Biological Aspects of Proteins* (Royal Institute of Chemistry, 1952).

disproved, however, by investigations on nutrition. Moreover, different proteins are not utilised by the organism to the same extent. Nutrition is therefore not merely a question of the energy content of the food and we now know that other factors such as vitamins are essential for normal growth and health.

The proteins are divided into two main classes :

- (1) **Simple Proteins** which on hydrolysis yield only amino-acids.
- (2) **Conjugated Proteins** which in contrast to the simple proteins are broken down hydrolytically not only to amino-acids but also to other substances termed *prosthetic groups*. An example of this type is the nucleoproteins whose prosthetic groups are nucleic acids. Other examples are given on p. 812.

The two types of protein will be discussed separately later, but an account will first be given of the general properties of the proteins. It is here only necessary to add that the simple proteins may be divided into two types :

Corpuscular Proteins.
Fibrous Proteins.

The corpuscular proteins are soluble in suitable solvents and include ovalbumin and ovoglobulin. The fibrous proteins on the other hand are insoluble and include keratin (from hair) and fibroin (from silk).

The first systematic protein investigations were carried out by the Dutch chemist G. J. Mulder, who, at the suggestion of Berzelius, introduced the name protein (Greek *protos* meaning first). It was early recognised that the chemical investigation of the proteins is attended by great difficulties. These arise partly from the complexity of the protein molecule and partly from the fact that the usual purification methods and criteria of purity cannot be applied to the proteins. The difficulty in isolating homogeneous products results from the characteristic sensitivity of the proteins, which are very readily altered by the process known as *denaturation* (p. 808). Heat, acids, alkalis, aqueous solutions of urea, etc. effect this change and convert "native" proteins into *denatured* proteins. In isolating proteins, therefore, the temperature is kept as low as possible and the proteins are maintained at a suitable pH (the iso-electric point of the protein).

Isolation and Purification. We have just seen that the instability of the proteins gives rise to special problems of isolation and purification. The proteins, for example, are sensitive to heat and consequently cannot be purified by distillation, the usual method for purifying a liquid or low melting solid. Crystallisation of proteins can be accomplished, though often with difficulty (p. 801), but its value as a method of purification is limited. The fibrous proteins are insoluble and cannot be crystallised.

The soluble proteins are generally obtained initially in the form of extracts from which they have to be precipitated, care being taken to

avoid denaturation. Precipitation is effected in a number of ways. Gentle warming is not satisfactory since there is a significant amount of decomposition, and the addition of acids such as hydrochloric acid is generally accompanied by denaturation. More satisfactory is the addition of organic solvents, particularly ethanol or acetone, although here, too, care is needed. Change of pH by the careful addition of alkali or acid is also effective and the protein is often precipitated at the isoelectric point. The method is reversible and involves only slight denaturation. Finally, "salting-out" by the addition of neutral salts, particularly ammonium sulphate or less frequently magnesium or sodium sulphate, furnishes a useful method and is employed for the fractional precipitation of proteins. During such precipitations the proteins retain their original properties, and, after having been filtered off, may be brought into solution again in their original condition. This method of reversible precipitation by neutral salts was introduced by Hofmeister, and depends not only on the solubility of the salts, but also on the specific action of the ions.

In recent years physical methods have proved of great service and ultra-centrifugation, electrophoresis, diffusion, chromatography, and freeze-drying are now used extensively to isolate and separate proteins.

In all purification processes it is essential to ensure that denaturation has not occurred and this is sometimes not easily done. One method is to show that the protein or precipitate is soluble and gives solutions whose properties are identical with those of the original solutions. Solubility can be used as a criterion of purity. This test is based on the fact that the solubility of a pure substance is independent of an excess of the solid material. Since the solubility of proteins is altered by traces of ions water is not used and concentrated salt solutions are preferred as solvents.

Crystallisation of Proteins.—The inability of proteins to diffuse through membranes is in strong contrast to the ease of diffusion of crystalloids, and led at first to the conclusion that proteins could not be obtained in a crystalline condition. This was later proved to be incorrect. On the one hand, protein crystals have been found in nature, as in the aleurone grains which are widely distributed in the seeds of plants; and, on the other hand, a number of proteins which do not naturally occur in the crystalline state have been converted into this form. For example, crystalline ovalbumin was obtained by Hofmeister in 1891 and horse serum albumin, hæmoglobin, and globulins from plant seeds were later prepared in the crystalline condition. In recent years thanks to the researches of J. H. Northrop and others many other proteins have been obtained crystalline.

It appears that the crystallisation of proteins in no way differs from that of crystalloids but, despite this similarity, it is not possible by recrystallisation to purify them to the same extent as other organic substances, owing to their sponge-like capacity for absorbing impurities from solution. Ovalbumin, for instance, can be recrystallised and was

thought to be a pure compound, but later experiments showed it to be a mixture. Indeed it is safe to say that few proteins have been obtained in a truly homogeneous condition. For this reason, some degree of uncertainty is attached to all investigations so far carried out in protein chemistry, and more especially in molecular weight determinations.

Molecular Weight Determinations.¹—Various methods have been used to determine the molecular weights of proteins. The values frequently quoted are those of T. Svedberg, obtained by his ultra-centrifuge method.²

Matter suspended in solution tends to form a sediment under the influence of gravity, but colloidal particles such as proteins remain in suspension. Sedimentation of protein particles does occur, however, when their aqueous solutions are placed in the ultra-centrifuge where fields as great as 500,000 times that of gravity can be obtained. The rate of sedimentation depends among other factors on the size and mass of the suspended particles and, on the assumption that the particles are protein molecules, Svedberg was able to calculate the molecular weight of a considerable number of proteins (see Table). Molecular weights have also been determined by osmotic pressure measurements and X-ray analysis and the results so obtained are in good agreement with those

Molecular Weight Determinations with the Ultra-Centrifuge, etc.

	Sedimentation Method.	Equilibrium Method.	Osmotic Pressure Method.	X-ray Analysis Method.
Pepsin	35,500	39,000	36,000	ca. 39,300
Lactoglobulin	41,500	38,000	35,000	40,000
Ovalbumin	44,000	40,500	44,000	..
Hæmoglobin (horse)	68,000	68,000	67,000	66,700
Serum albumin (horse)	70,000	68,000	73,000	< 82,800
Excelsin	295,000	..	214,000	305,800

obtained by the ultra-centrifuge. Svedberg's method has the advantage that it affords a method for determining not only the weight but also the shape and size of protein molecules.

It is of interest that the tobacco mosaic disease virus, which is a protein, has the amazing molecular weight of about 20,000,000.

Soluble proteins may often exist as molecules in the ordinary sense of the word, but sometimes the apparent molecular weight varies with change in concentration or hydrogen ion concentration. For example, casein (M.W. 96,000) on dilution dissociates into particles (M.W. 32,000).³ The process is reversible, the particles (M.W. 32,000) reuniting to form the particles (M.W. 96,000). Similar changes are observed when the pH of protein solutions is altered.⁴ This *reversible dissociation* of protein

¹ P. Johnson, *Ann. Reports*, 1946, 43, 30, 52.

² *Chem. Rev.*, 1937, 20, 81.

³ D. C.

Carpenter, *J.A.C.S.*, 1935, 57, 129.

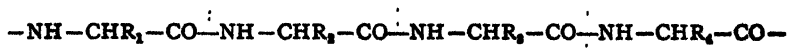
⁴ T. Svedberg, *Compt. rend. trav. lab. Carlsberg*, 1930, 18, No. 5.

particles into smaller particles shows that in the larger particles the sub-units are bound by weak bonds such as hydrogen linkages, etc. It may be, however, that dissociable proteins are only produced by the methods used to prepare them and that they do not exist as such in the tissues.

Structure of the Proteins.—The complexity and the sensitivity of the proteins to chemical and physical change has rendered the elucidation of their structure a formidable problem. Since the pioneer work of Emil Fischer and Hofmeister at the beginning of the century a vast amount of research has added and is adding to our knowledge of the proteins, but much remains puzzling and obscure. Nevertheless encouraging results of great significance have been obtained in recent years by both chemical and physical methods.

The proteins are hydrolysed by acids, bases, or enzymes into *L*-amino-acids and, as was shown by the brilliant researches of Emil Fischer and Hofmeister, they are long-chain peptides. To elucidate the complete structure of the proteins, therefore, it is essential to know (1) the nature and number of the constituent amino-acids, how they are linked together, and the order in which they occur in the molecule, and (2) how these peptide chains are spatially arranged.

As has already been stated some two dozen α -amino-acids have been obtained from the proteins (p. 233). By suitable methods the amino-acid composition of many proteins has been determined and the problem to be settled is how these acids are linked together and in what order. There is no doubt that the amino-acid residues are linked to one another by the *peptide bond* ($-\text{NH}\cdot\text{CO}-$).

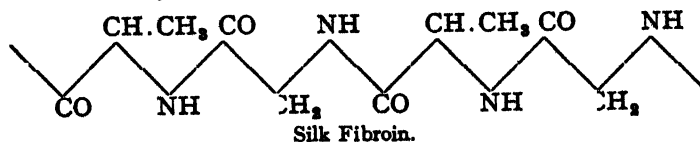


Among the evidence for this the following may be cited :

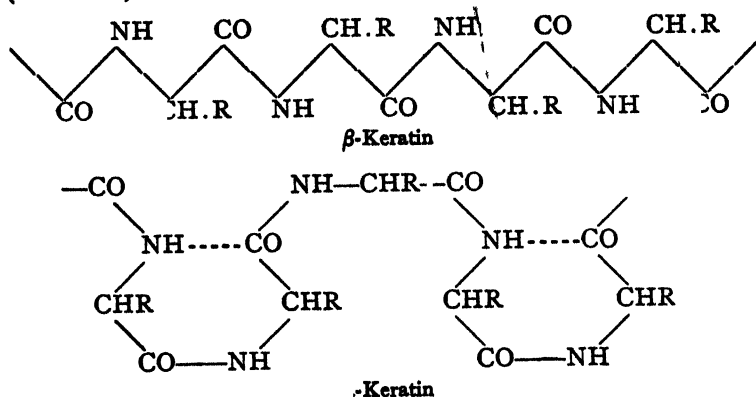
1. Peptides are frequently encountered when the proteins are incompletely hydrolysed.
2. The synthetic peptides obtained by Fischer from optically active amino-acids of the *L*-series are hydrolysed by the enzymes of the digestive tract.
3. In native proteins few free amino and carboxylic groups can be detected, but by the hydrolysis of proteins amino and carboxyl groups are liberated at approximately the same rate.
4. Erepsin acts on peptides and it is highly probable that it attacks the peptide bond. It is found that protein which has been partially broken down to peptides by pepsin is to a large extent hydrolysed by erepsin.

It can scarcely be doubted, therefore, that most of the nitrogen in proteins is present in the peptide bond. There must, however, be other important bonds, since pepsin, which does not attack peptides, acts on proteins and it is not yet known which bond it attacks.

The picture of the protein molecule as a long-chain peptide fits in with the structure of the fibrous proteins such as *silk fibroin* and the conception that these compounds are composed of fibrous molecules has been demonstrated by X-ray measurements.¹

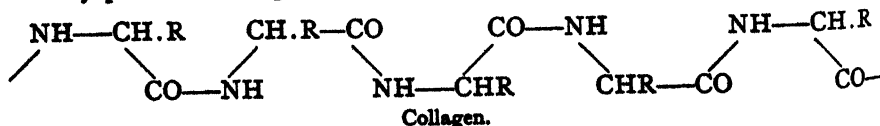


Most fibrous molecules, however, have not such a simple structure. In hair, for instance, *keratin* gives X-ray photographs quite unlike that of silk, and it seems that in this case the protein is not fully extended (α -keratin). Stretched hair (β -keratin), however, has a structure like silk fibroin. On removal of the tension the keratin returns to its normal state (α -keratin).



β -Keratin is thus pictured as an extended peptide chain and α -keratin as a folded structure such as that shown above. The unstretched form can be made to shrink to considerably less than its usual length, the molecules then existing in a *super-contracted form*. This is supposed to be due to the fission of weaker cross linkages.

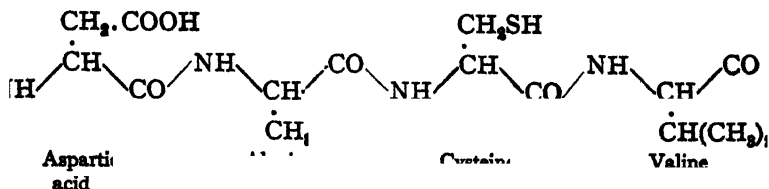
Myosin, the chief protein of muscle, has a structure similar to that of keratin. The fibres of the tendrous and connective tissue, on the other hand, give the same type of X-ray photograph which is quite distinct from that of keratin; the same photograph is obtained with *gelatine*. Astbury pictured collagen as shown in the figure :



Other structures have, however, been advanced.²

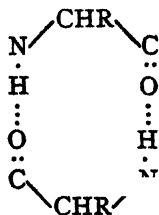
¹ For the interesting results of X-ray investigations on proteins, see W. T. Astbury, *Ann Reports*, 1938, 35, 198. ² W. T. Astbury, *Proc. Roy. Soc.*, 1947, B134, 303.

An important consequence of the structure assigned to the proteins—long peptide chains of α -amino-acid units—is that the amino-acid side-chains project from the chain on alternate sides. This can be seen by inspection of the β -keratin formula given on p. 804. If it is postulated that the side-chains on each side of the main chain are chemically similar and, further, that the side-chains on one side differ chemically from those on the other, certain characteristics of the proteins can be accounted for. This is exemplified by a protein fragment containing the residues of aspartic acid, alanine, cysteine, and valine in which the two polar groups (COOH and SH) are on one side of the chain and the alkyl groups ($[\text{CH}_3$ and $(\text{CH}_3)_2\text{CH}]$) are on the other.



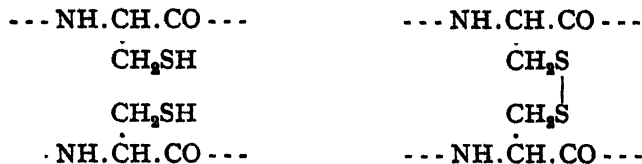
The protein molecule thus possesses two surfaces which differ chemically one containing polar groups such as COOH , NH_2 , CH_2SH , and the other non-polar groups such as CH_3 and other alkyl groups. In this way the adsorption of proteins on water and on non-aqueous surfaces is explained, the polar groups being attracted by the water molecules and the non-polar groups by organic liquids.

In contrast to the fibrous proteins, X-ray examination of the globular proteins gives no evidence of the presence of a long-chain configuration, though it can scarcely be doubted that in the globular proteins peptide chains do exist, but only as the components of a folded or three-dimensional system. It must be admitted that our knowledge of the detailed structure of proteins is still very incomplete and that no entirely complete and satisfactory theory of protein molecular structure has yet been advanced. There is, however, considerable evidence against the existence of any



fundamental distinction between fibrous and corpuscular proteins. In other words both fibrous and corpuscular proteins are fundamentally peptides of high molecular weight in which the atoms in the chains are held together by the ordinary valency forces. Other weaker forces, however, play an important role and determine the spatial arrangement of the peptide chains. Prominent among these is the hydrogen bond which is very much weaker than the normal chemical bond. These

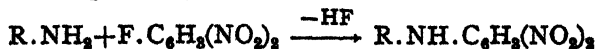
bonds occur between the amino and carbonyl radicals in neighbouring peptide chains and are partly responsible for the organisation and orientation of the peptide chains. Other bonds are electrovalent linkages formed between acidic and basic amino-acids, and disulphide linkages resulting from the dehydrogenation of two cysteine residues.



The significance of these weaker linkages is emphasised in the conclusions of L. Pauling and C. Niemann¹: "It is our opinion that polypeptide chain structures of proteins with hydrogen bonds and other interatomic forces (weaker than those corresponding to covalent bond formation) acting between polypeptide chains, parts of chains, and side-chains is compatible not only with the chemical and physical properties, but also with the detailed information about molecular structure in general which has been provided by the experimental and theoretical researches of the last decade."

One other problem of protein structure remains to be discussed, namely, the order of the amino-acids in the peptide chains. This problem will require an enormous amount of experimental work before it is finally solved, but sufficient progress has been made to lead to the hope that known methods may be developed and will lead to eventual success.

The method adopted to determine the order of the amino-acids is based on examination of the structures of the partial hydrolysates of proteins, *i.e.* the hydrolytic peptide fragments. It is known, for example, that silk on hydrolysis gives the dipeptides glycine-alanine and glycine-tyrosine and a slight insight into the structure of silk fibroin is thus obtained. Another example is found in the determination of the amino-acid order in Gramicidin S (p. 250). In an extension of the method a protein is partially broken down and the terminal groups of the peptides "marked" or "labelled" by means of a suitable reagent. This mode of attack is exemplified by the work of F. Sanger, who condensed peptides obtained by the hydrolysis of insulin with 1-fluoro-2:4-dinitrobenzene. The terminal amino-groups of the peptides condense with the reagent to give 2:4-dinitrophenyl (DNP) derivatives.



The peptide derivatives are then hydrolysed further and from insulin the following products are obtained:

DNP-glycylisoleucine
 DNP-glycylisoleucylvaline
 DNP-glycylisoleucylvalylglycine.

¹ *J.A.C.S.*, 1939, 61, 1860.

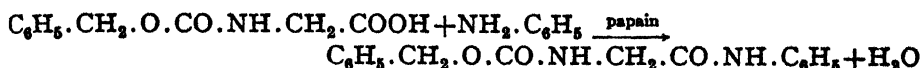
One fragment of the insulin molecule must contain amino-acids in the following order :

glycine-isoleucine-valine-glycine.

By extending this method the complete structures of the two peptide chains in insulin have been established,¹ thus making possible the elucidation of the structure of the insulin molecule (p. 811).

There is now sufficient chemical and physical data for models of the protein molecules to be constructed and tested, and this line of research is being actively pursued.²

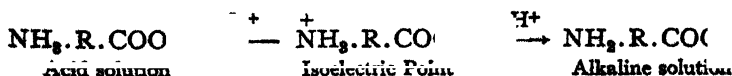
Synthesis of Proteins.—When it is realised that many proteins contain some 300 amino-acid residues in the molecule the immensity of the task of synthesising proteins is evident. It would seem that the most promising approach to the problem is that of obtaining facile methods for the synthesis of polypeptides (see p. 247). The laboratory problem is also obviously related to the process by which proteins are synthesised in living cells where the syntheses are probably controlled by enzyme action. A pointer that this is indeed the case comes from work on the enzyme *papain* which is known to hydrolyse proteins: it has now been shown that this enzyme can take part in the synthesis of peptide linkages.³ For example :



Similar results have been obtained with other enzymes. It can scarcely be doubted that further work on enzymatic synthesis will yield results of the greatest significance.

Properties of the Proteins.—The soluble proteins behave in some ways like crystalloids, but many of their most characteristic properties such as non-diffusibility through membranes are colloidal. This dual role is not altogether surprising when it is remembered that the proteins are large-sized ions, pepsin, for instance, which is a protein of comparatively small molecular weight, having a radius of 22A (cf. Na⁺ 0.95A). The proteins therefore exhibit the properties both of colloids and *ampholytes* or amphoteric electrolytes.

The proteins contain in the peptide chains some acidic and basic amino-acids and, owing to the free amino and carboxyl groups, are ampholytes and like the amino-acids have dipolar ion properties. In acid solution they are transferred to the cathode and in alkaline solution



¹ F. Sanger and H. Tuppy, *Biochem. J.*, 1951, 49, 463, 481. F. Sanger and E. O. P. Thompson, *ibid.*, 1953, 53, 353. ² See H. N. Rydon, *Ann. Reports*, 1951, 48, 238. ³ Max ergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, 1937, 219, 707.

The proteins are thus positively charged in acid solution and negatively charged in alkaline solution. It is clear that there must be an intermediate stage where the proteins are electrically neutral and do not migrate to the poles of an electric field. The hydrogen ion concentration at which this occurs is known as the isoelectric point (see p. 240), and on Bjerrum's hypothesis, a protein at this point is completely ionised. The isoelectric point is a characteristic constant for each protein and is of great importance since a protein at this point has special properties. For instance, the solubility of a protein is at a minimum at the isoelectric point, as are other properties such as viscosity, swelling, etc. At this point, too, the optimum condition obtains for the heat coagulation of a large number of proteins; serum globulin, indeed, is precipitated without heating at the isoelectric point.

The proteins are thus dipolar ions containing a large number of positive and negative charges which come from amino and carboxyl groups not participating in the peptide linkages. The free amino groups are provided by aspartic and glutamic acids and the basic groups by the guanido residue of arginine and the ϵ -amino-group of lysine.

As has already been mentioned, albumins and globulins undergo *denaturation* under the influence of heat, ultra-violet light, addition of alcohol or acetone, etc. A familiar example of this is the irreversible coagulation of egg white when heated. Denaturation, which is generally though not invariably irreversible, results in complete insolubility at the isoelectric point, change in the magnitude of the specific rotation, and loss of biological activity (*e.g.* enzymes lose their catalytic activity). Denaturation is a complex process which is not yet fully understood. There seems little doubt, however, that fundamentally it is caused by a loosening or fission of weaker linkages (hydrogen bonds, salt-linkages, etc.) with the result that the protein structure becomes less compact and the peptide chains more disorganised.¹

The presence of proteins in a solution modifies the properties of dissolved substances, owing to adsorption, hydration, etc. For example, proteins prevent the deposition of difficultly soluble salts from solution. This fact is of great biological importance and accounts for the existence of dissolved calcium salts in the body fluids. On the other hand, the presence of proteins lowers the solubility of many easily soluble salts. Proteins are also efficient protective colloids; in minute amounts they protect suspensoids from precipitation by electrolytes. The number of milligrammes of a protein which is just insufficient to protect 10 c.c. of a standard colloidal gold solution from precipitation by 1 c.c. of a 10 per cent. solution of sodium chloride, is known as the *gold number* of the protein concerned (Zsigmondy). This number is characteristic for each individual protein.

Detection of Proteins.—The presence of proteins is shown by a number of reactions, although no single reaction is in itself a reliable test.

¹ H. Neurath *et al.*, *Chem. Rev.*, 1944, 34, 157.

The reactions of proteins are divided into precipitation and colour reactions. For determining the presence of proteins in animal fluids certain precipitation reactions only may be employed. Whereas the colour reactions depend on the occurrence of specific chemical groups in the protein molecule, and are therefore given also by the corresponding non-protein hydrolytic products, the precipitation reactions are due to the colloid nature of the protein and these alone give reliable information as to the presence of protein as such. Precipitation reactions are accordingly employed in medical science for the detection of protein matter in animal fluids (*e.g.* urine). Colour reactions should be applied exclusively to pure protein solutions.

Precipitation Reactions.—Proteins are coagulated when heated in faintly acid solution, especially in the presence of neutral salts. In *Heller's Test* concentrated nitric acid is gently poured down the side of the test-tube containing the protein solution. The acid forms a lower layer and a white disc of precipitated protein appears at the junction of the two liquids.

Proteins are precipitated by the addition of *salts of heavy metals*, such as ferric chloride, ferric acetate, copper sulphate, mercuric chloride, basic lead acetate, and by the *alkaloid reagents*, *e.g.* phosphotungstic acid and phosphomolybdic acid (in the presence of mineral acid), tannin, hydroferrocyanic acid, and picric acid. As phosphotungstic acid effects complete precipitation, it is frequently employed for the removal of dissolved protein, more especially of basic protein. The reactions with tannin and hydroferrocyanic acid are also very sensitive. Protein in urine is detected by precipitation with a 20 per cent. solution of sulphosalicylic acid.

Colour Reactions.—There are many colour tests for proteins most of which are given by certain amino-acids. A notable exception to this is the biuret test.

Biuret Reaction.—Addition of a dilute solution of copper sulphate to an alkaline solution of a protein gives a purplish-violet colour (see p. 355). A positive reaction indicates the presence of the peptide linkage. The biuret reaction is not a specific test for protein, since it is given by certain other substances (see p. 249).¹

Millon's Test.—A solution of mercuric nitrate and nitrite in nitric acid containing a little nitrous acid gives on boiling with protein a white precipitate which turns red. The reaction is given by phenols unless both ortho positions are substituted and with proteins is due to the presence of tyrosine.

Ninhydrin Reaction.—Proteins and all α -amino-acids heated with triketohydrindene hydrate (ninhydrin) give a blue colour (see p. 241).

Xanthoproteic Reaction.—A protein solution with strong nitric acid gives a yellow colour, occasionally in the cold, but usually only after heating. On addition of excess of sodium hydroxide the liquid becomes

¹ H. Schiff. *Ber.* 1866. 20. 208: 1867. 20. 2455.

reddish-brown, whereas with excess of ammonia it turns an orange colour. The reaction depends on the presence of tyrosine.

The Hopkins-Cole Reaction.—With a mixture of concentrated sulphuric acid and glyoxalic acid (or a solution of glyoxalic acid in glacial acetic acid) proteins give a reddish violet colour, slowly in the cold, but more rapidly on warming. The reaction is due to the presence of tryptophan groups and hence is not given by gelatin.

SIMPLE PROTEINS

As has already been mentioned, proteins may be divided into two main classes, each with a number of sub-groups. The simple proteins, which will be discussed first, on hydrolysis yield only amino-acids or derivatives. Some simple proteins, however, are known to contain small quantities of carbohydrates. They are sub-divided as follows.

(1) *Albumins.*—Simple proteins soluble in pure water and salt solutions. Examples: ovalbumin (egg albumin), serum albumin, and lactalbumin (from milk).

(2) *Globulins.*—Sparingly soluble in pure water, but soluble in neutral salt solutions. Examples: serum globulin, ovoglobulin (from egg yolk), edestin (from hemp seed), and fibrinogen (from blood).

(3) *Glutelins.*—Insoluble in all neutral solvents, but readily soluble in very dilute acids and alkalis. Example: glutelin (from wheat).

(4) *Prolamins.*—Insoluble in water, absolute alcohol, and other neutral solvents, but soluble in 70-80 per cent. alcohol. Examples: gliadin (from wheat), and zein (from maize or wheat).

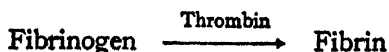
(5) *Scleroproteins.*—Completely insoluble in all neutral solvents. These substances are the principal organic constituents of the skeletal structure of animals. They cannot be dissolved without undergoing chemical change, and differ from other proteins chiefly in their resistance towards chemical reagents. Examples: keratin (from hair, horn, feathers, etc.), elastin (from ligament), collagen (from tendon), and fibroin (from silk).

(6) *Histones.*—Soluble in water and insoluble in very dilute ammonia; in the absence of ammonium salts insoluble even in excess ammonia. The histones are basic proteins of low molecular weight. On hydrolysis they give a number of amino-acids among which the basic ones predominate. Example: the histone of the thymus gland.

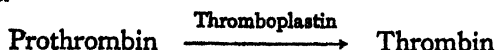
(7) *Protamins.*—Strongly basic peptides which are simpler than the proteins included in the preceding groups. They form stable salts with strong mineral acids and on hydrolysis yield comparatively few amino-acids, among which the basic ones predominate. They are the simplest natural proteins. Examples: salmine (from salmon) and clupein (from herring).

Some Individual Simple Proteins.—*Myosin* is the most important protein in muscle and plays a part in the phenomenon known as *rigor mortis*.

Fibrinogen is contained in the blood of all vertebrates and clots under the influence of certain enzymes. This important process occurs in the presence of calcium salts and the enzyme *thrombin* (*thrombase*), whereby the fibrinogen is converted into the fibrillar network form, *fibrin*, i.e., the soluble protein fibrinogen is converted into the insoluble fibrin.

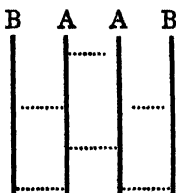


The immediate precursor of the enzyme is *prothrombin*, which is converted by the enzyme thromboplastin into thrombin. Calcium ions are necessary for this reaction.



The anti-coagulant heparin in conjunction with its co-factor may inhibit the formation of thrombin and thus prevent coagulation. Dextran sulphate acts similarly.

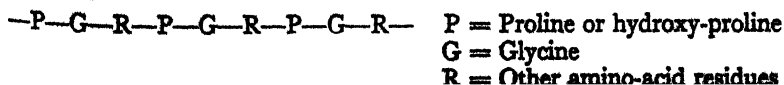
Insulin is the hormone of the pancreas and controls the combustion of carbohydrates in the animal body. Its absence gives rise to diabetes. Insulin has a molecular weight of approximately 48,000, but at a *pH* under 4 or above 7.5 it breaks down into sub-units whose molecular weight is approximately 12,000. It appears from the work of Sanger and others (p. 806) that each sub-unit contains four peptide chains composed of 2 identical A (acid) chains and 2 identical B (basic) chains held together by —S—S— bridges. Moreover in the A chains there are 20 amino-acid residues and 4 half cystine groups, while the B chains contain 30 amino-acids and 2 half cystine groups. Insulin therefore contains a unit which



may be represented by the annexed diagram, in which the cystine cross-linkages are indicated by dotted lines. Since the sequence of the amino-acids in the peptide chains has been established (p. 806) our knowledge of the structure of the insulin molecule is well advanced.

Another protein hormone is *thyroglobulin*, the hormone of the thyroid gland. On hydrolysis with baryta it yields thyroxine (p. 859), but with proteolytic enzymes it gives diiodotyrosine (iodogorgoic acid).

Collagen.—Collagen is the structural protein of connective tissue and constitutes the major part of tendons and ligaments. It is rich in glycine, proline, and hydroxy-proline. The amino-acid sequence seems to be something like the following :



When boiled with water collagen passes more or less readily into solution, the soluble product being known as *gelatin* (glutin).

Keratins are the structural proteins of hair, wool, and nails. They have a high cystine content and the cystine residues play an important role in the insolubility of the keratins.

Fibroin.—Fibroin is the principal insoluble protein of silk along with a minor constituent, the protein *sericin*. Fibroin is mainly built up from four amino-acids: alanine, glycine, serine, and tyrosine.

Spongin (from the common sponge) and *gorgonin* (the coral protein) are, like keratin, insoluble and resistant to enzyme action.

CONJUGATED PROTEINS

The conjugated proteins contain the protein molecule united to a prosthetic group such as a nucleic acid or carbohydrate.

(1) *Nucleoproteins*.—Compounds of one or more protein molecules with nucleic acid. They occur in cell nuclei.

(2) *Glycoproteins or Mucoproteins*.—Compounds of the proteins with a substance or substances containing a carbohydrate group other than a nucleic acid. Example: mucin.

(3) *Phosphoproteins*.—Proteins in which the prosthetic group is phosphoric acid. Example: casein (from milk) and vitellin (from egg yolk).

(4) *Chromoproteins*.—Proteins containing hæmatin or some similar substance. Examples: hæmoglobin and hæmocyanin.

(5) *Lipoproteins*.—Compounds in which a protein molecule is linked to a lipid.

Nucleoproteins

Nucleoproteins are compounds of proteins with nucleic acids and are of great biological importance occurring as they do in all plant and animal cells. They were so named because they were early recognised as being important constituents of cell nuclei. They are now known to occur also as components of cell cytoplasm and the viruses causing many plant and animal diseases are nucleoproteins. They are acid in character and are denatured by heat. In spite of intensive research the manner in which the component proteins and nucleic acids are united is not yet established and undoubtedly varies in different cases; in some the linkages seem to be electrovalent, whereas in others they are stronger and almost certainly covalent.

Corresponding to the two main types of nucleic acids there are two types of nucleoproteins. **Ribonucleoproteins** occur in the cell cytoplasm, and are soluble in physiological saline. **Deoxyribonucleoproteins** occur in the cell nucleus. They are insoluble in physiological saline, but dissolve in 10 per cent. sodium chloride solution.

Virus Proteins.—Both plant and animal viruses have been the subject of intensive research in recent years and the discovery that certain plant viruses are protein macromolecules is of great interest to the organic chemist. In 1935 W. M. Stanley at the Rockefeller Institute for Medical Research isolated a crystalline substance from tobacco plants infected with the disease known as tobacco mosaic. This substance proved to be the tobacco mosaic virus and is a nucleoprotein. It has the properties characteristic of the proteins except that its molecular weight is much greater than usual—between 15 and 20 million. By means of the electron microscope it has been shown that the virus has a rod-like shape of approximate dimensions 15×280 A.

All viruses so far isolated are nucleoproteins, those of plant origin consisting of protein and ribonucleic acid, while those of animal origin contain ribonucleic acid or deoxyribonucleic acid or both together with protein and usually lipids.

Glycoproteins

Glycoproteins are conjugated proteins containing sugars or their derivatives. As might be expected, their nitrogen content (11.7 to 12.3 per cent.) is less than that of the true proteins. The group consists essentially of the *mucins*, present in the mucous membranes, together with the related compounds, pseudo-mucins, mucoids and chondroproteins. It has already been stated on p. 319 that ordinary mucins yield *glucosamine* on hydrolysis; in a similar manner the mucin from frog spawn yields *galactosamine*. The *chondroproteins* contain chondrosamine, a sugar of a different configuration, which appears to be closely related to galactosamine.

The *mucins* are widely distributed in nature and are known to be constituents of mucus and saliva. They are markedly acid in character, do not dissolve in pure water, but dissolve readily in alkali carbonates and ammonia. From these solutions they are precipitated by the addition of excess of acetic acid. They are not coagulable by heat. The mucins are very closely related to the chondroproteins. Of the latter, the most carefully investigated representative is *chondromucoid*, which with collagen is one of the chief constituents of cartilage. On hydrolysis it yields protein and *chondroitin sulphuric acid*, an acid ester of sulphuric acid with carbohydrate, containing also amino-acid residues. When chondroitin sulphuric acid is boiled for a short time with acids, it is hydrolysed further to sulphuric acid and a sulphur-free component *chondrosin*.

Phosphoproteins

The most important of this class of proteins is *casein* the phosphoprotein of milk. The protein is not homogeneous and on precipitation gives a number of fractions, mainly α - and β -casein. It is hydrolysed

to the constituent amino-acids and phosphoric acid, and on partial hydrolysis yields phosphoserylglutamic acid. Like fibrinogen, casein undergoes clotting, both by acids and by the enzyme *chymosin* (rennet). The mechanism of clotting is still not understood, but it is known that calcium ions are necessary for the reaction.

The souring of milk in summer, *i.e.* acid clotting, is to be distinguished from the curdling produced by rennin. The former is the direct result of the fermentation of the lactose by micro-organisms, leading to the formation of lactic acid which precipitates the caseinogen (see above). The residual clear liquid is known as sour whey. On the other hand the residual liquid from cheese is known as sweet whey, owing to the absence of acid.

Hæmoglobins

These are compounds of proteins with pigments containing iron. *Hæmoglobin*, the red colouring matter of the blood of vertebrates, is the chief constituent of red blood corpuscles. It is built up from a protein, *globin*, and a prosthetic compound, *hæm*. Hæm contains iron, and will be described in detail on p. 815 *et seq.* It is probable that the bloods of different animals contain different hæmoglobins. With oxygen, carbon monoxide and other gases, hæmoglobin combines to give loose addition compounds, such as oxyhæmoglobin and carboxy-hæmoglobin. The most important of these is oxyhæmoglobin, which contains one molecule of hæmoglobin to one of oxygen. It readily gives up its oxygen again and thus plays an essential part in the respiration of the vertebrates. When blood is allowed to stand in air the unstable oxyhæmoglobin, in which iron is in the ferrous state, readily changes into the stable methæmoglobin, containing ferric iron. Hence the latter has been largely used in analyses and other investigations on the colouring matter of blood. Hæmoglobin is not salted out from a neutral solution by the addition of sodium chloride or magnesium sulphate, but only by saturation with a mixture of magnesium and sodium sulphates.

Under the influence of acids methæmoglobin decomposes into globin and hæmatin. With hydrochloric acid, for example, it yields globin and an ester-type of compound of hæmatin and hydrochloric acid, known as *hæmin*. The latter is described in the following chapter, but it may be noted that its property of separating in characteristic reddish-brown microcrystalline needles is of importance for the detection of blood stains in forensic medicine.

The compound formed by union of hæmoglobin with carbon monoxide is more stable than oxyhæmoglobin; and the poisonous character of carbon monoxide is due to the ease with which it displaces oxygen from oxyhæmoglobin, thus preventing oxygen from being carried to the tissues.

X

Natural Colouring Matters

The following chapter is devoted to the chemistry of certain natural colouring matters and is divided into three sections, the first dealing with porphyrin derivatives of blood and leaves, the second with the carotenoids and the third with anthocyanins of flowers and berries.

PORPHYRIN DERIVATIVES

HÆMOGLOBIN

The two most conspicuous and wide-spread pigments of nature are **hæmoglobin**, the colouring matter present in the red corpuscles of blood, and **chlorophyll**, the colouring matter of green plants and leaves. The functions of the two substances are in absolute contrast, hæmoglobin participating in *oxidative* reactions while chlorophyll under the action of light takes part in the *reduction* of atmospheric carbon dioxide to carbohydrates. This functional distinction, however, only serves to emphasise the striking structural similarity of the two compounds, both being derivatives of a complex stable structure composed of four pyrrole nuclei. These structures are known as **porphyrins** and are exemplified by formula I, **protoporphyrin**. Hæmoglobin as we have already seen is a conjugated protein formed by the combination of the protein *globin* and the prosthetic group, the pigment **hæm**. Inspection of the formula of hæm (II) and chlorophyll (p. 824) reveals clearly the similarity of their chemical structure. Both contain four substituted pyrrole rings linked together symmetrically by four methine (CH) groups. Such a system of four unsubstituted pyrrole rings linked by four methine groups is known as the **porphine ring**. Porphyrins are simply substituted porphines. In hæm all the eight β -positions of the pyrrole nuclei are substituted, the 1, 3, 5, and 8-positions by methyl groups, the 2- and 4- by vinyl groups, and the neighbouring 6- and 7-positions by propionic acid residues. In chlorophyll the eight β -positions are likewise substituted but in a different manner. C_2 has a vinyl group, but C_4 has the ethyl radical attached to it. The propionic acid residue at C_6 is absent and is replaced by a substituted cyclopentanone ring, while the acid group at C_7 is esterified with the long-chain alcohol phytol. Finally one of the pyrrole rings in chlorophyll is partially hydrogenated.

As is mentioned later there are two chlorophylls, *a* and *b*, which differ only slightly in their chemical constitution, chlorophyll *a* having a methyl group at C_2 while chlorophyll *b* has an aldehyde grouping.

A fundamental difference between hæm and chlorophyll is that hæm is a derivative of ferrous iron and chlorophyll of magnesium.

Hæmoglobin very readily absorbs one molecular proportion of oxygen to yield **oxyhæmoglobin**, in which form oxygen is carried in the blood stream to various parts of the organism, where it is utilised with regeneration of hæmoglobin. When blood is removed from the organism, the oxyhæmoglobin contained in it changes into **methæmoglobin** in which oxygen is more firmly held. When heated with acetic acid methæmoglobin breaks down to globin and a brownish-red pigment **hæmatin**, $C_{34}H_{32}N_4O_4FeOH$; if sodium chloride is also present, a hydroxyl group of hæmatin is replaced by chlorine and **hæmin**, $C_{34}H_{32}O_4N_4FeCl$, is formed. Hæmin is thus the chloride of hæmatin, both compounds containing iron in the ferric state.

An important advance was made in 1926 when Hill and Holden successfully separated the *natural* globin from hæmoglobin and showed that the undenatured protein combined with neutral hæmatin (p_H 5 to 10) to form methæmoglobin. Similarly with hæm (p_H 9.0) it yields hæmoglobin itself.

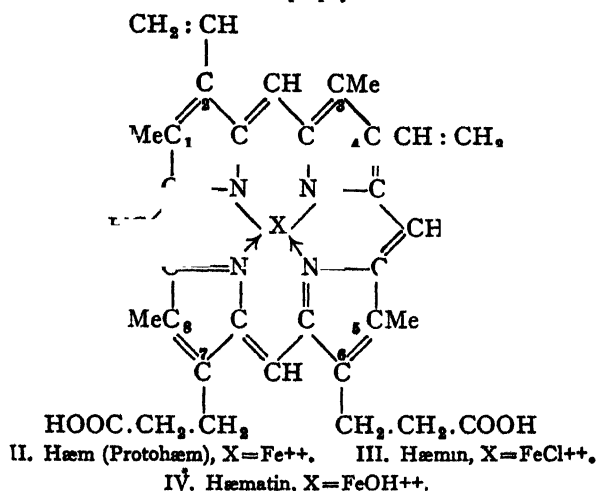
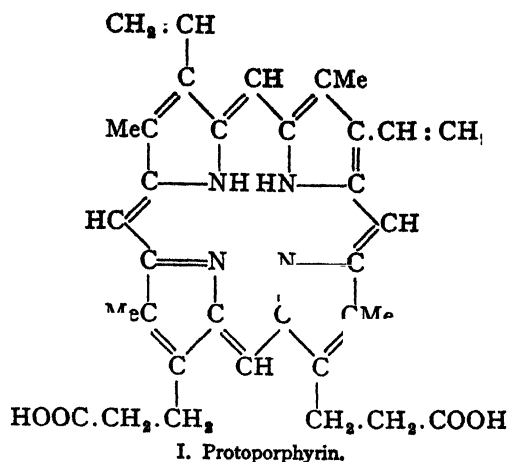
The porphyrins obtained by the removal of iron from hæm or hæmatin exhibit minor differences in composition according to the acid reagent employed for the purpose (conc. H_2SO_4 , HCl , HBr in glacial acetic acid). They are readily identified spectroscopically and can again be transformed into their complex iron salts, hæmins, which show a close spectroscopic resemblance to natural hæmin. Iron can usually be introduced without difficulty so that hæmins and porphyrins must have similar molecular structures. Hence it will be seen that reliable information as to the nature of hæmoglobin may also be obtained by investigating hæmin and the corresponding iron-free **hæmatoporphyrin** obtained from hæmin by the action of hydrobromic or hydrochloric acid.

Structure of Hæmin.—The structure of hæmin has been deduced from the degradations of porphyrins (Piloty, Küster) and the magnificent synthetic work of Hans Fischer and his co-workers. It contains trivalent iron, two of the valencies being used to link the iron to the rest of the molecule with the help of two co-ordinate bonds and the third to the chloride ion. It is an artificial product. Inspection of the formula (III) shows the iron is surrounded by the conjugated porphyrin ring which accounts for the intense colour, characteristic absorption spectra, and comparative stability of hæmin.

The degradation experiments may conveniently be divided into two sections depending on whether the porphyrin ring remains intact or is broken.

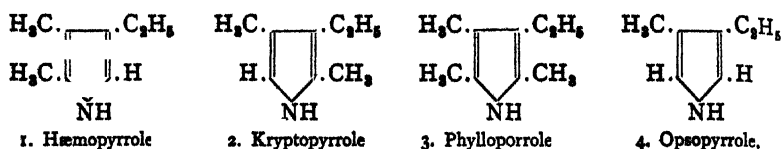
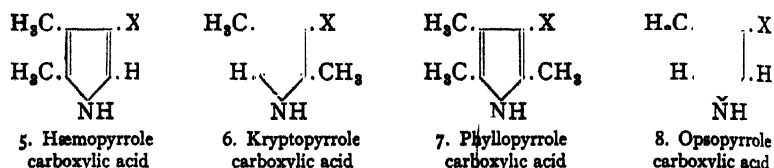
(1) *Degradations with Porphyrin Ring Intact.*—**Protoporphyrin** (formula I) is an important porphyrin prepared from hæmin by treatment with dilute acid, which replaces the central $FeCl^{++}$ group by $2H$ and leaves the vinyl groups intact. Under more vigorous conditions with hydrogen bromide in acetic acid hæmin yields **hæmatoporphyrin** resembling protoporphyrin in structure but with two $CHOH.CH_3$ groups in place of the vinyl groups. Protoporphyrin on reduction passes into

mesoporphyrin (formula I with the two vinyl groups replaced by ethyl groups). Finally, the two propionic acid residues in mesoporphyrin may be converted into ethyl groups with loss of two molecules of carbon



dioxide by heating the compound in a high-boiling solvent (*pyrolysis*). In this way ætioporphyrin-III or mesoætioporphyrin is produced.

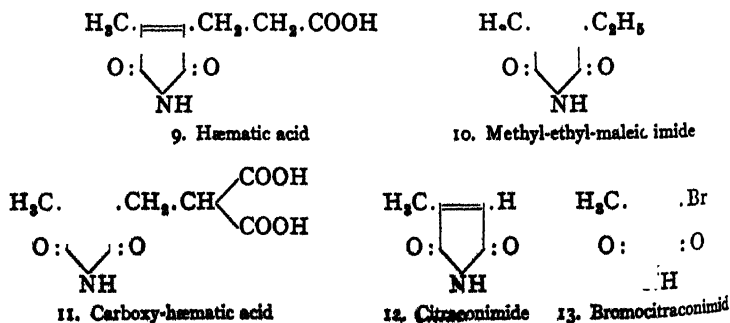
(2) *Breakdown of the Porphine Ring*.—The most successful disruptive method is the energetic reduction with hydriodic acid and acetic acid first used by Nencki. In this way O. Piloty obtained a mixture of pyrrole bases from which he isolated *hæmopyrrole*, *kryptopyrrole*, *phyllopyrrole*, and *opsopyrrole* as well as the corresponding acids in which the ethyl group of the bases are replaced by propionic acid residues. These acids were later prepared in the pure state by Hans Fischer and his co-workers. The formulæ of the disruptive reduction products of hæmin thus isolated are given on the following page.

Reductive Disruption Products of Hæmin. Hæmopyrrole Bases*Hæmopyrrole Carboxylic Acids (X=CH₃, CH₂, COOH)*

Good yields of alkylated decomposition products are obtained from hæmin by heating it under pressure at 230° with alcoholates, especially potassium methoxide. The latter reagent leads exclusively to the formation of phyllopyrrole and phyllopyrrole carboxylic acid, thus confirming the above results.

Another valuable process is the *chromic acid oxidation of hæmin and its derivatives* first carried out by Küster. The related oxidative disruption of the porphyrins has given much information about their structure.

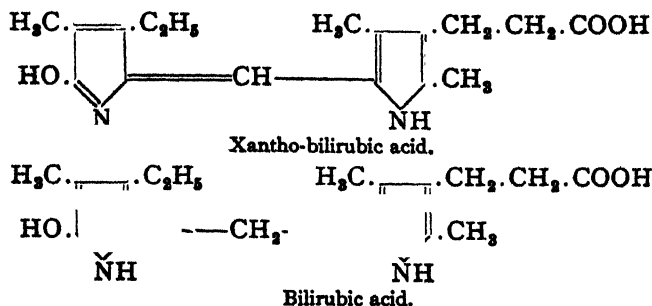
Küster isolated **hæmatic acid** by oxidation of the colouring matters of blood and bile, and it has in addition been obtained from many porphyrins. The oxidative conversion of these compounds into hæmatic acid (9) and similar derivatives not only proved of great value in determining their constitution, but also led to a more systematic examination of the products of reductive disruption (p. 817) and to the isolation of pyrrole-carboxylic acids from this source. Hæmatic acid was synthesised by Küster from acetoacetic ester.

Oxidative Disruption Products

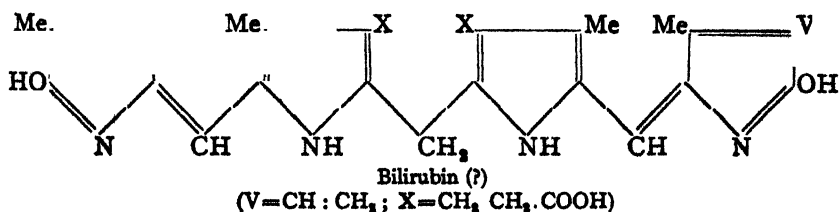
A further oxidation product is the carboxylated hæmatic acid formulated provisionally as in 11 above, which on being heated to a high temperature yields hæmatic acid and methyl-ethyl-maleinimide. It is obtained by oxidation of *uroporphyrin* and its synthetic analogue *isroporphyrin*.

Finally, citraconimide (12) and bromocitraconimide (13) may be mentioned; these were obtained with hæmatic acid from deuteroporphyrin, dibromo-deuteroporphyrin and bromoporphyrin.

Dipyrrole degradation products of hæmin and of porphyrins are not yet known, although *billirubic acid* was discovered almost at the same time by Piloty and H. Fischer among the reduction products of the colouring matter of bile. The constitution of this compound together with that of its dehydrogenated derivative are given below.



The brown colouring matter of bile, *billirubin*, $\text{C}_{33}\text{H}_{36}\text{O}_8\text{N}_4$, also resembles hæmin in yielding hæmatic acid on oxidation with chromic acid. It is probably a degradation product of hæmoglobin and is believed to have the structure

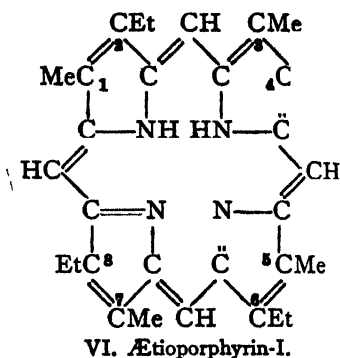
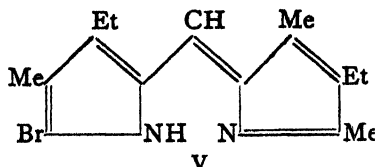


Comparison with the formula for hæmin given on p. 817 shows that the arrangement of the side chains attached to the pyrrole nuclei is the same in the two compounds.

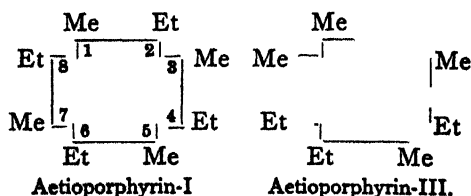
A consideration of the disruption products described in the foregoing pages shows the complexity of the formulæ which the porphyrins must possess, but Küster as early as 1912 from his knowledge of the breakdown products and the elementary analysis of hæmin succeeded in advancing a formula for hæmin which differs from that now accepted only in the relative positions of a vinyl and a methyl group attached to one of the four pyrrole nuclei. Küster's pioneer work was consummated

in 1929 by Hans Fischer's synthesis of hæmin,¹ one of the greatest achievements in the history of organic chemistry.

Synthesis of Hæmin. Hans Fischer's synthesis of hæmin was part of the ambitious programme which resulted in the derivation of the constitutions of hæm, hæmin, and the porphyrins by brilliant synthetic work in which successful methods were developed for condensing substituted pyrroles to give various types of *dipyrrolyl-methenes* (e.g. V). Two of these furnish the necessary four pyrrole rings and can be converted into porphyrins of known structure. For example, kryptopyrrole (p. 818) may be condensed by treatment with bromine to give a bromodipyrrolyl-methene (V), two molecules of which with formic or sulphuric acid undergo further condensation by loss of HBr between the 2-methyl and 2-bromo substituents to form ætioporphyrin-I (VI).



By these and similar reactions Fischer synthesised a number of ætioporphyrins, the structures of which he represented briefly as follows by a bracket formula showing the arrangement of the substituents in the pyrrole nuclei composing the *porphin ring*. The unsubstituted compound, *porphin*, has also been synthesised. Ætioporphyrin-I,



having an alternating system of methyl and ethyl groups, proved identical with the ætioporphyrin prepared from *coproporphyrin*. On the other hand, ætioporphyrin-III was identified with the ætioporphyrin from *hæmoglobin*. It

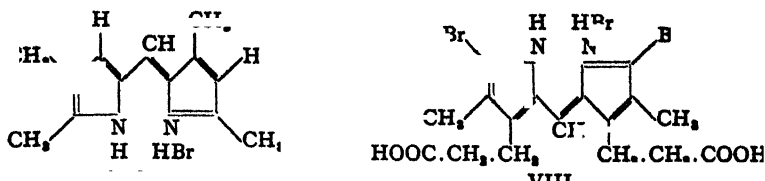
contains two adjacent ethyl groups at 6 and 7, derived as will be seen from the formulæ given above from the two propionic acid groups present in hæmatin and protoporphyrin.

As will be seen from inspection the ætioporphyrins closely resemble the porphyrins obtained by loss of iron from hæmin, the vinyl groups and propionyl residues being replaced by ethyl groups. Another method of building up the porphyrin ring is to fuse 2 : 2'-dibromopyrrolylmethenes with 2 : 2'-dimethyldipyrrolylmethenes in succinic acid.

¹ H. Fischer and K. Zeile, *Ann.*, 1929, 478, 98.

With the knowledge of the structures of the ætioporphyrins and with the help of the technique evolved in the course of their syntheses Fischer proceeded to synthesise hæmin.

In the synthesis of hæmin 2 : 3-dimethylpyrrole readily condenses with 2 : 4-dimethylpyrrole-5-aldehyde to give the dipyrromethene hydrobromide (VII). Another dipyrromethene hydrobromide (VIII) is obtained from kryptopyrrole-carboxylic acid (p. 818) by treatment with bromine accompanied by loss of a methylene group. When heated at 180-190° in succinic acid VII and VIII condense to form a mixture of

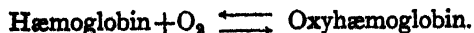


products from which is isolated deuteroporphyrin, *i.e.* protoporphyrin in which both vinyl groups are replaced by hydrogen. This is converted into the corresponding deuterohæmin by heating it in acetic acid with ferrous acetate with the addition of a little sodium chloride and a drop of concentrated hydrochloric acid. Conversion to the deuterohæmin is necessary because deuteroporphyrin is so much less reactive than the iron compound that it does not undergo the following step in the synthesis. Acetylation of the two free positions is now effected by acetic anhydride and stannic chloride and the resulting diacetyl-deuteroporphyrin then reduced with alcoholic potassium hydroxide to hæmatoporphyrin ($\text{CH}_3\text{CO} \rightarrow \text{CH}_2\text{CHOH}$). On heating hæmatoporphyrin at 105° in a high vacuum two molecules of water are lost, the hydroxyethyl groups being thereby changed into vinyl groups to yield protoporphyrin (p. 816) which gives hæmin on introduction of iron into the molecule.

All the above formulæ contain a continuous alternation of single and double bonds, thus accounting for their strong colour. As in the case of benzene derivatives, the compounds are resonance hybrids and the exact bond arrangement cannot be depicted with certainty.

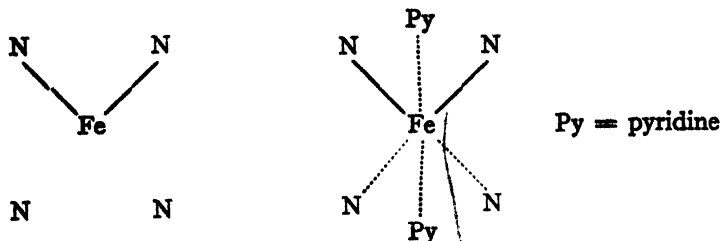
Chemical Constitution of Hæmoglobin, etc.

Hæmoglobin is biologically important because of its efficiency as a transporter of oxygen in animal systems according to the equation :

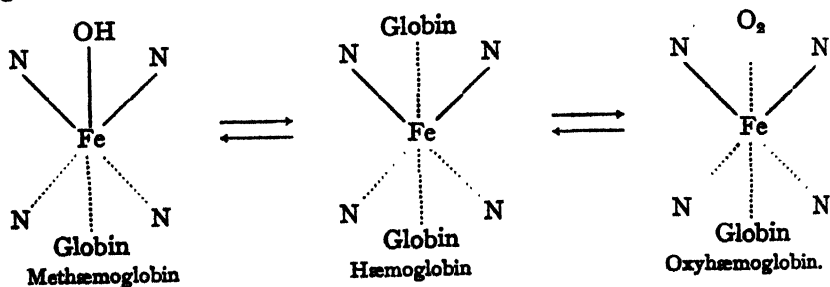


Insight into the mechanism of this and related reactions has been obtained by the determination of the chemical constitutions of hæmoglobin, oxyhæmoglobin, methæmoglobin, etc. Hæmoglobin, as we have seen, is a conjugated protein in which globin is linked to hæm, which is a compound

of protoporphyrin and ferrous iron. In the above oxygenation the iron remains in the ferrous condition, but nevertheless participates in the process. It also participates in the linkage of the hæm molecule to globin. Now it is known that ferrous iron normally has a covalency number of 6, whereas in hæm it is 4. This strongly suggests that compounds such as hæm will readily add on substances capable of co-ordination and this is indeed observed, hæm for instance, readily giving pyridine-hæmochromogen as shown by the abbreviated formulæ below in which only the nitrogen atoms of the porphyrin ring are shown.



In similar fashion the iron in hæmoglobin is coordinated with the iminazole rings of histidine, the main amino-acid of globin.



With oxygen an equilibrium is established between hæmoglobin and oxyhæmoglobin as depicted above, one of the iron-globin linkages being displaced by an iron-oxygen bond. In the oxidation of hæmoglobin to methæmoglobin, however—an oxidation which can be effected *in vitro* by oxidising agents such as potassium ferricyanide—the iron is oxidised to the ferric condition.

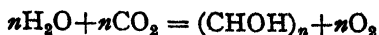
Why hæm should require the particular protein globin to give hæmoglobin its characteristic property of combining reversibly with oxygen is still a mystery, but the structural advances outlined above are perhaps sufficient to show that progress is being made towards a solution of the problem.

The chloroplasts of plants consist of a colloidal mixture of colourless substances and two types of pigments, namely the chlorophylls and the carotenoids. Chemically the two classes are quite distinct, the chlorophylls being complex pyrrole derivatives and the carotenoids nitrogen-free polyene pigments.

CHLOROPHYLL¹

Chlorophyll occurs as the chief pigment in all green vegetable matter and its importance is comparable to that of water and oxygen for without it life as we know it could not exist. Chlorophyll plays a vital catalytic role in the process known as *photosynthesis* in which water and carbon dioxide combine to form carbohydrates with the evolution of oxygen. Animals require but cannot synthesise carbohydrates and consequently depend ultimately on plants to provide them. The significance of photosynthesis and chlorophyll is therefore evident.

Chlorophyll has another vital function in maintaining the oxygen-carbon dioxide balance in the atmosphere. Plants and animals breathe oxygen from the air and exhale carbon dioxide. This carbon dioxide is converted by photosynthesis into organic material and at the same time



oxygen is emitted. It is clear that without photosynthesis the atmosphere would be charged with carbon dioxide at the expense of oxygen.

Chlorophyll *a*, $\text{C}_{55}\text{H}_{72}\text{O}_5\text{N}_4\text{Mg}$, is a bluish-black solid forming greenish-blue solutions, and Chlorophyll *b*, $\text{C}_{55}\text{H}_{70}\text{O}_6\text{N}_4\text{Mg}$, a greenish-black solid forming pure green solutions.

On the large scale chlorophyll is obtained by extracting the dried powdered leaves of the stinging nettle, followed by purification of the crude material. The pigment so obtained was shown first by Tswett and later by Willstätter to be a mixture of chlorophyll *a* and *b* in the ratio of 2:1. Chlorophyll *a* and *b* are most effectively separated chromatographically and in this way Winterstein and his co-workers obtained pure chlorophyll *b* for the first time.

Chemistry and Structure of Chlorophyll

Much of our knowledge of the chemistry of chlorophyll is due to Willstätter, who derived methods for its extraction from leaves and made a very thorough examination of its degradation products. The information thus gained was subsequently extended by the synthetic work of Hans Fischer on the porphyrins derived from the colouring matter of blood. The two fields of investigation were shown to be closely related since chlorophyll, porphyrins such as hæmin, and their degradation products all possess the porphin ring structure of four pyrrole rings (p. 815). The work culminated in the brilliant synthesis of hæmin and the advancement of a probable formula for chlorophyll.

Chlorophyll contains about 2.7 per cent. of magnesium and on hydrolysis yields the alcohol phytol, $\text{C}_{20}\text{H}_{40}\text{O}$ (see p. 816) in quantities corresponding to about a third part of its molecule, and methyl alcohol. The other hydrolysis product is a carboxylic complex containing four

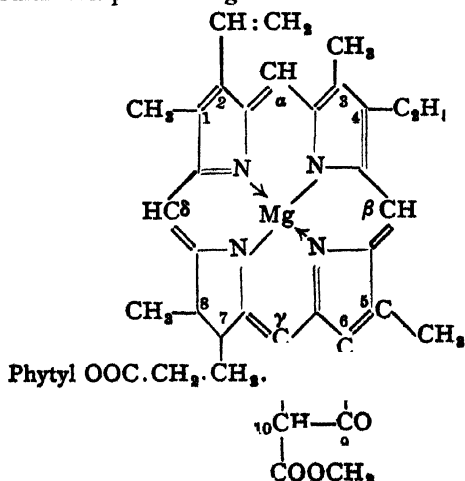
¹ Willstätter and Stoll, *Untersuchungen über Chlorophyll* (Springer, Berlin, 1913). For surveys of the chemistry of chlorophyll see C. C. Steele, *Chem. Rev.*, 1937, 29, 1; H. Fischer, *ibid.*, p. 41.

pyrrole nuclei. This structure has already been encountered in the porphyrins described in the previous chapter.

As already mentioned our knowledge of the chemistry of chlorophyll owes much to the parallel investigations carried out on the colouring matter of blood, and reference should be made to the account given of the degradation products of hæmin (p. 816 *et seq.*). A definite relationship between the molecular structures of chlorophyll and hæmin was first indicated by the researches of Hoppe-Seyler in 1879 and of Schunck and Marchlewski fifteen years later, which led to the isolation from both sources of coloured disruption products, porphyrins. This conclusion was supported by the work of Nencki and of Willstätter on the reduction of hæmin and chlorophyll to mixtures of pyrroles (see hæmopyrrole, p. 818); and by Willstätter's oxidation of the phylloporphyrin prepared from chlorophyll, which was found to yield methyl-ethyl-maleinimide and hæmatic acid, the same products as had previously been obtained by Küster from the colouring matter of blood. In addition, Willstätter succeeded in degrading chlorophyll to an ætioporphyrin which was believed to be the same as that derived from hæmin, although it was later established by Fischer that the compounds in question were closely related but not identical.

Mention has already been made of the extensive investigations of Fischer on porphyrins and their derivatives, which led to the synthesis of many members of this group, including the ætioporphyrins of chlorophyll and hæmin. From the information thus obtained, supplemented by the researches of Conant, Stoll and others, a provisional formula for chlorophyll *a* (see below) has been advanced.

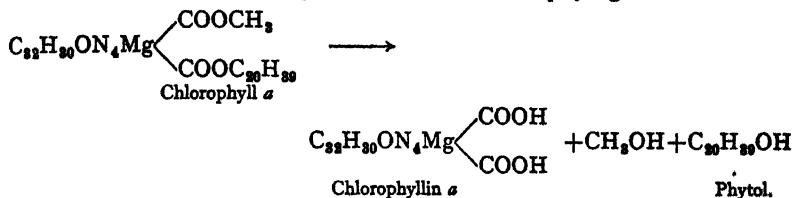
The relationship between chlorophyll and hæmogoblin may be summarised in the following terms. Chlorophyll is a wax, whereas hæmoglobin is a molecular compound of globin with the carboxylic acid hæm.



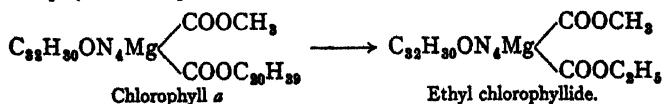
Chlorophyll, as an ester, contains not only phytol but also methyl alcohol. Its nucleus is a dihydroporphin ring (the two extra hydrogens being placed at 7 and 8) and the side chains include one vinyl group instead of the two present in hæmin. The propionic acid group in position 6 of hæmin has become a β -ketopropionic acid group, which has united with the γ -carbon atom and undergone oxidation to form the isocyclic ring characteristic of chlorophyll. Finally, magnesium has replaced the co-ordinately bound iron.

Chlorophyll *b* is represented by Fischer as having the above formula in which the methyl group at 3 is replaced by a formyl group ($\cdot\text{CHO}$). It is much more difficult to obtain in the pure state and has been less investigated.

Decomposition of Chlorophyll by Alkalis and Acids¹.—Chlorophyll, as has already been stated, is a diester containing methyl and phytyl groups. On hydrolysis with alkalis the alcoholic residues are removed, with the formation of salts of the carboxylic acids known as chlorophyllins (*a* and *b*). These salts still contain magnesium and are chlorophyll-green in colour.



A change in the chlorophyll structure affecting the phytyl group has been found to take place if, during the extraction of the pigment from leaves, the materials are allowed to remain in contact for a considerable time. A secondary reaction then occurs owing to the presence in the leaves of an enzyme, *chlorophyllase*, which brings about partial alcoholysis of the chlorophyll, replacing the phytyl group by an alkyl radical corresponding to the alcohol used for the extraction. The resulting diesters are known as chlorophyllides, that obtained with ethyl alcohol being *ethyl chlorophyllide*. Unlike chlorophyll, which is amorphous in nature, the chlorophyllides deposit in the form of microcrystalline plates.



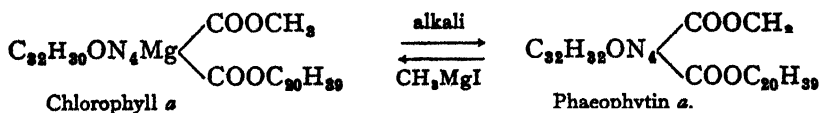
The above compounds still retain the vinyl group at position 2, the two extra hydrogen atoms at 7 and 8, and the complete isocyclic system (6, 9, 10, γ) of the chlorophyll molecule. The magnesium atom is comparatively stable to vigorous treatment with alkalis, although very easily removed by acids. On brief treatment with boiling alcoholic potassium hydroxide the product first formed from chlorophyll *a*, known

¹ For a schematic representation of the changes described in the following pages see Table — — —

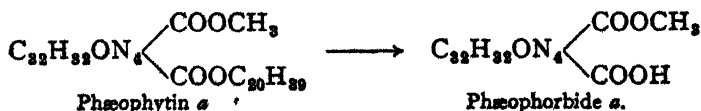
as *isochlorophyllin a*, contains *three* carboxyl groups, due to rupture of the isocyclic ring (compare chlorin *c*, p. 827). Concentrated alcoholic alkali at higher temperatures, up to 240° , brings about a rearrangement of the hydrogen atoms, 2H being detached from positions 7 and 8, and added to the vinyl group at 2, converting it into an ethyl group. At the same time the carboxyl groups are progressively reduced by loss of CO_2 to two and finally to one. All these acids still contain one atom of magnesium for every four atoms of nitrogen, and are grouped together under the name of **phyllins**, some of them being named from their colour, *e.g.* **rhodophyllin**, (red). The corresponding oxygen-free derivative, **ætiophyllin** $\text{C}_{30}\text{H}_{34}\text{N}_4\text{Mg}$, can be obtained from rhodophyllin after eliminating the last carboxyl group by heating in small quantities with soda-lime. In this final product it is obvious that the oxygen atoms have no part in the formation of the metallic complex. The magnesium in chlorophyll and its derivatives is therefore supposed to be united to nitrogen by covalent and co-ordinate valency bonds as indicated in the formula on p. 824. The above chemical changes, however, are more readily followed by use of the magnesium-free compounds.

Under the influence of acids all phyllins lose magnesium to yield compounds known as **porphyrins**. Except in the case of the **ætioporphyrins** corresponding to ætiophyllin, these are acidic as well as basic in properties. Mixtures of porphyrins are purified by a method devised by Willstätter, according to which a fractional separation is effected by extracting the compounds in ethereal solution with hydrochloric acid of varying concentrations. This process takes advantage of the different basicities of the individual constituents.

Chlorophyll itself behaves in a similar manner when treated with dilute mineral acids, the ester groups remain unaffected but magnesium is removed leaving **phæophytins** (*a* and *b*), the change being accompanied by an alteration in colour from green to olive-green.

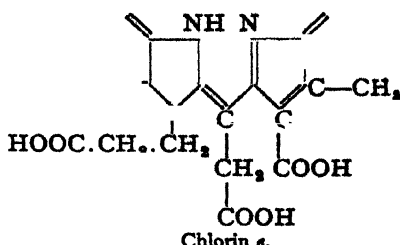
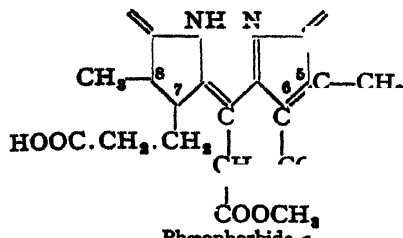


It is an interesting fact that chlorophyll can easily be regenerated from phæophytin by bringing the latter into reaction with methyl magnesium iodide. Vigorous treatment with concentrated acids detaches the more easily hydrolysed phytyl group, forming **phæophorbide**, containing one free carboxyl group and one methyl ester group.



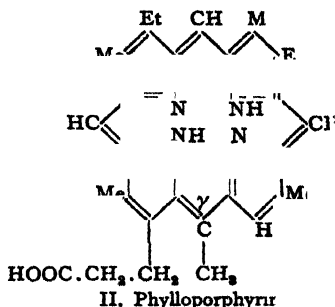
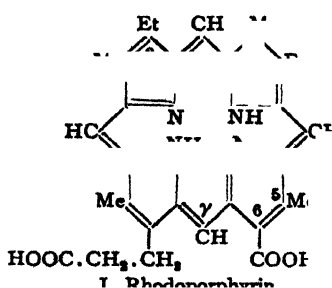
A more fundamental modification of the structure takes place when phæophorbide *a* is heated for 30 seconds with methyl alcoholic potassium hydroxide. Two changes then occur, the methyl ester group is hydrolysed

and the isocyclic ring is disrupted with the formation of a third carboxyl group. Fischer represents the rearrangement undergone by this portion of the molecule as follows, the rest of the structure being as shown for chlorophyll *a* (p. 824), except for the replacement of covalent magnesium by two atoms of hydrogen. The resulting compound is chlorin *e*,



(*phytychlorin e*), a tricarboxylic acid. In the same way chlorophyll *b* may be degraded to the tricarboxylic acid rhodin *g*.

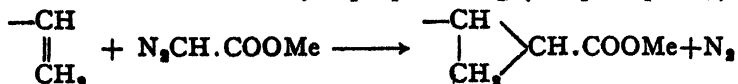
Still more drastic treatment of chlorophyll or the above intermediate products by heating in a sealed tube with alcoholic alkali leads to the successive elimination of CO_2 from the carboxyl groups, accompanied by loss of the two hydrogen atoms at 7 and 8 and the saturation of the vinyl group at 2. In this way are obtained **rhodoporphyrin**,



$\text{C}_{30}\text{H}_{32}\text{N}_4(\text{COOH})_2$, **pyrroporphyrin**, $\text{C}_{30}\text{H}_{32}\text{N}_4(\text{COOH})$, and **phylloporphyrin**, $\text{C}_{31}\text{H}_{33}\text{N}_4(\text{COOH})$. The structures of the first and third are shown above; pyrroporphyrin is a lower homologue of phylloporphyrin, having H in place of the CH_3 -group attached to the γ -carbon atom.

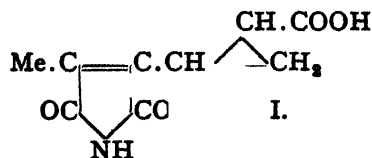
The last carboxyl group can be eliminated, either by pyrolysis in high boiling solvents or by distillation with soda lime, yielding **pyroaetioporphyrin** and **phylloaetioporphyrin** (formulae as in I and II above, but with carboxyl groups replaced by hydrogen). The latter compound is thus a higher homologue of the former. It can be converted into pyrroaetioporphyrin by heating with sodium ethoxide, when the γ -methyl group is displaced by hydrogen. This reaction also explains the production of two series of degradation products from chlorin *e*, one of which contains the γ -methyl group and the other does not.

Reference to the above formulæ shows clearly how methylethyl maleic imide and hæmatic acid arise from the oxidation of porphyrins with chromic acid. The presence of a free methine hydrogen atom at position 6 in pyrro- and phyllo-porphyrins was established by brominating the compounds, followed by oxidation and the isolation of bromocitraconimide (see p. 818). The actual arrangement of the methyl, ethyl and propionic acid substituents around the porphin ring was determined by the brilliant syntheses of porphyrins carried out by H. Fischer. The existence of a vinyl group in methyl phæophorbide and the ester of chlorin *a* has been proved by treatment with methyl diazoacetate, when the vinyl double bond reacts to form a cyclopropane ring (compare p. 689).



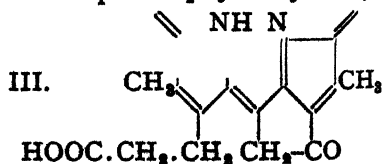
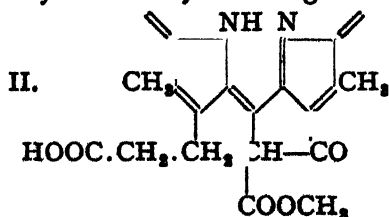
which can be isolated in the form of methylmaleicimide-cyclopropyl carboxylic acid (I) on vigorous oxidation of the addition product.¹

The above degradations of chlorophyll and phæophorbide to porphyrins did not serve to establish the presence of a porphin ring in chlorophyll itself, because the drastic treatment with alkali might conceivably have led to a breakdown of the molecule followed by a secondary synthesis of a porphyrin. A direct connection between the two series has been deduced by other methods.



Thus by use of milder conditions Conant² found that when heated with diphenyl at 180° to 250° (*pyrolysis*) phæophorbide and chlorin *a* lost 1 and 2 molecular proportions of CO₂ respectively, and that the latter compound also gave rise to two isomeric products, one of which was a porphyrin. Fischer and Conant independently reduced chlorophyll derivatives using hydriodic acid and glacial acetic acid at 60° (Fischer) or catalytic hydrogenation in presence of platinum (Fischer and Conant). In this way a leuco-compound was obtained from phæophorbide *a* which on aerial oxidation gave a series of phæoporphyrins, *e.g.* phæoporphyrin *a*,³ C₃₄H₃₄O₅N₄; similarly, chlorin *a* yielded chloroporphyrins.

Phæoporphyrin *a*, which has been assigned formula II (with the upper part of the molecule as for rhodo- or phyllo-porphyrin) can be readily decarboxylated to give the stable compound phylloerythrin, III.

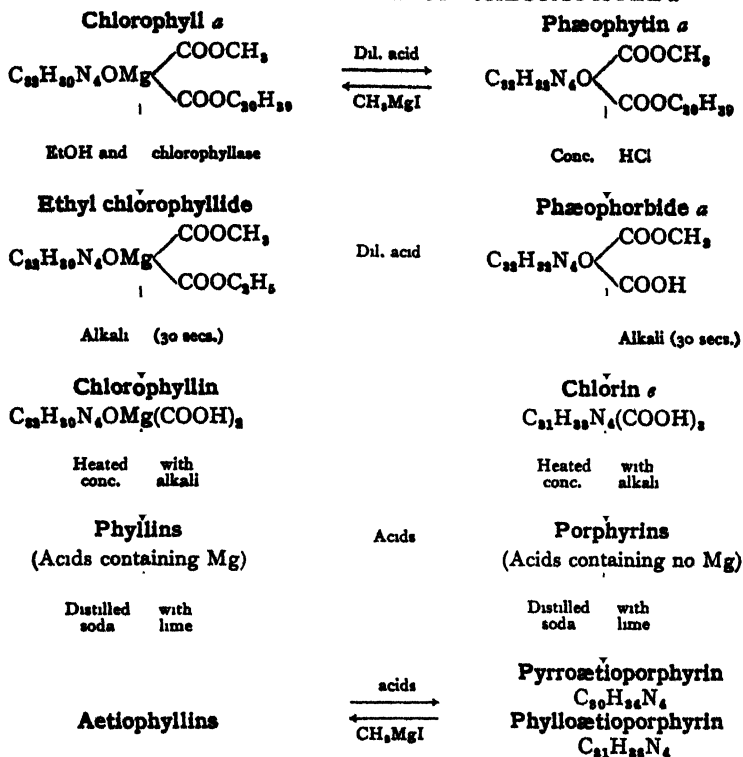


¹ H. Fischer and Medick, *Ann.*, 1935, 517, 245. ² J. B. Conant and J. F. Hyde, *J.A.C.S.*, 1929, 51, 3668. ³ The figure 5 indicates the number of oxygen atoms. The formula given represents the free acid, actually isolated as the monomethyl ester.

Phylloerythrin is a ketone; it yields an oxime and can be reduced to *deoxyphylloerythrin* ($\text{CH}_2\text{.CO}\rightarrow\text{CH}_2\text{.CH}_2$). When treated with sodium ethoxide in the presence of air phylloerythrin is converted into phyllo-, pyrro- and rhodoporphyrins by disruption of the isocyclic ring, a change which establishes the position of the ketonic oxygen as being attached to C9.

The formation and properties of phylloerythrin, the structure of which has also been confirmed by synthesis, constitute an important argument

DEGRADATION PRODUCTS OF CHLOROPHYLL *a*



in support of the porphin-ring character of the chlorophyll molecule, and throw further light on the structure of the attached isocyclic ring. The close biological relationship between chlorophyll and phylloerythrin is emphasised by the fact that the latter was first discovered by Marchlewski in ox-bile, and that it occurs in the fæces of ruminants, especially in sheep dung. It is proved to be a porphyrin by its chemical properties and absorption spectrum, and it can also be obtained directly from chlorophyllide and the phaeophorbides (both of the chlorophyll type) by prolonged boiling with 20 per cent. hydrochloric acid.

The main outlines of the structure of chlorophyll as expressed in the formula on p. 824 are accepted by all workers in this field, but there is still some discussion as to the arrangement of the double bonds.

CAROTENOIDS¹

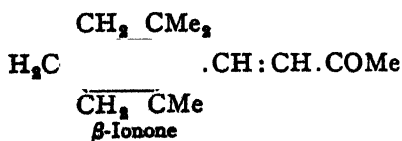
The carotenoids or yellow constituents accompanying the green colouring matter of leaves are found associated with chlorophyll in the chloroplasts. They are widely distributed in plants and a number of them are obtained as by-products in the preparation of chlorophyll. Structurally, the carotenoids belong to the class of compounds known as *polyenes*, and their characteristic colour and sensitiveness to atmospheric oxygen is due to the presence in the molecules of a series of conjugated double bonds.

All green leaves and various other parts of plants contain these nitrogen-free crystalline pigments, which possess many properties in common but may be separated by taking advantage of their different solubilities or by chromatographic adsorption on lime or aluminium oxide. Among the chief members of this group are the *hydrocarbons*, α -, β - and γ -carotenes and lycopene; the *alcohol*, xanthophyll; and the *carboxy derivatives* crocetin and bixin.

Much of the fundamental work in this field was carried out by P. Karrer, R. Kuhn, and their co-workers.

The Carotenes, $C_{40}H_{56}$, are coloured, highly unsaturated hydrocarbons which are present in butter, carrots, and green leaves, as well as in a number of flowers and fruits. "Carotene" was isolated from carrots as early as 1831, but a hundred years elapsed before R. Kuhn showed it to be a mixture of three closely related forms, a dextrorotatory α -carotene and the optically inactive β - and γ -carotenes, which can be readily separated by chromatographic adsorption on calcium hydroxide from a petroleum solution.² The carotenes are intimately related to vitamin-A, into which they are transformed by hydrolysis in the organism.

After the empirical formula had been determined by Willstätter, the catalytic hydrogenation of carotene (as well as of lycopene and xanthophyll) was examined by Zechmeister in 1927. β -Carotene and



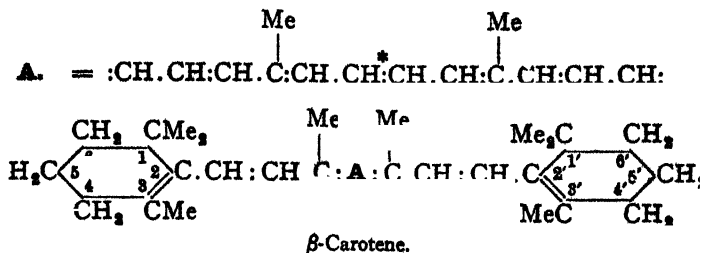
xanthophyll were found to contain eleven ethylenic double bonds and were concluded to have two cyclic groups in their molecules. The cyclic structures were later shown to be β -ionone rings,

this possibility having been suspected from the smell of violets which is developed when carotene undergoes auto-oxidation.

β -Carotene.—The complete structure of β -carotene, m.p. 187° , was deduced by Karrer³ from the behaviour of the compound on oxidation. With cold aqueous potassium permanganate, β -ionone was formed, and at a higher temperature a mixture of acetic acid (4 mols.), 1 : 1-dimethylglutaric acid, dimethylsuccinic acid and a little dimethylmalonic acid

¹ R. F. Hunter, *The Carotenoid Group in Chemistry of the Carbon Compounds*, edited by E. H. Rodd, vol. IIa, p. 353. ² See I. M. Heilbron, *J.S.C.I.*, 1937, 160 T. ³ P. Karrer and co-workers, *Helv. Chim. Acta*, 1930, 23, 1084; 1931, 24, 1033. R. Kuhn and H. Brockmann, *Ann.*, 1935, 526, 95.

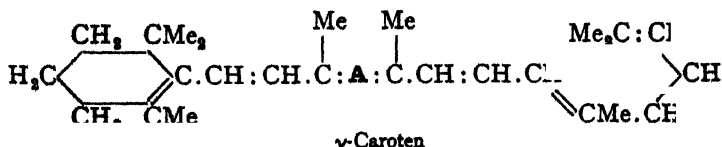
was obtained. These dibasic acids are also formed by the oxidation of β -ionone, and acetic acid is known to result (in many cases quantitatively) from methyl groups attached to a polyene chain. Ozonisation led to the production of *geronic acid*, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CMe}_2 \cdot \text{COOH}$,



owing to rupture of the β -ionone ring. It has been found that the conjugated central portions of the molecules of polyene pigments are generally built up of isoprene units arranged symmetrically about the middle (*) of the chain. In order to save space they are conveniently formulated as shown in the preceding structure for β -carotene, in which the central portion is given separately as A. The structure assigned has been confirmed by several syntheses.

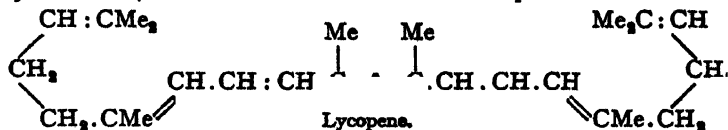
α -Carotene melts at 183° and is optically active. Karrer represents it as having the same formula as the β -isomeride except that one of the two $\text{:CH} \cdot \text{CH} \begin{matrix} \text{CMe}_2 \cdot \text{CH}_2 \\ \text{CMe} \cdot \text{CH} \end{matrix} \text{CH}_3$ β -ionone rings is replaced by an α -ionone ring. The asymmetric carbon atom of this ring which is attached to the polyene chain accounts for the optical activity. On ozonisation the α -ionone ring gives rise to *isogeronic acid*, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CMe}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$. α -Carotene has been synthesised.

γ -Carotene, m.p. 178° , resembles the β -compound in being optically inactive. One half of its structure is that of β -carotene, the other half is an open-chain arrangement which is also present in lycopene (see below). γ -Carotene is present in very small quantities in the carotene mixture, but is readily separated by adsorption on aluminium hydroxide.



Only those polyenes, such as the carotenes, which possess at least one unmodified β -ionone ring in the molecule, appear to be capable of undergoing conversion into vitamin-A in the organism and hence of promoting growth. The closely related xanthophylls in which the rings are hydroxylated, are not physiologically active, nor is the open chain hydrocarbon lycopene.

Lycopene, $C_{40}H_{56}$, is isomeric with carotene and was first isolated from the tomato in 1873. It is a dark red compound which also occurs in rose hips, the berries of the bitter sweet and other plants. The molecule is assigned the following aliphatic structure in which both of the ionone rings present in β -carotene are severed to form open chains.



Xanthophylls

The xanthophylls are hydroxy- or keto-carotenoids and are widely distributed in nature.

Lutein, $C_{40}H_{54}(OH)_2$, is 5 : 5'-dihydroxy- α -carotene and is found with carotene in the green parts of all plants. Its structure was established mainly by the work of Karrer and his school.

Zeaxanthin, $C_{40}H_{54}(OH)_2$, is the corresponding dihydroxy-derivative of β -carotene, i.e. it is 5 : 5'-dihydroxy- β -carotene. It occurs in fruits but is most readily obtained from maize. Zeaxanthin occurs as the dipalmitic ester, *physalene*. Its di-epoxide is *violaxanthin*, the pigment of the yellow pansy.

Cryptoxanthin, $C_{40}H_{55}OH$, is 5-hydroxy- β -carotene. It occurs in the sunflower, capsicum, and yellow maize. It is of interest since it exhibits provitamin-A activity.

Capsanthin, $C_{40}H_{55}O_3$, is obtained from red pepper (paprika). It contains two hydroxyl and one ketone group and its structure has been established.¹

Astacene, $C_{40}H_{48}O_4$, is the distinctive pigment of the *Crustacea*, and was first isolated from lobster shell and characterised by Kuhn and Lederer. Its constitution as 4 : 5 : 4' : 5'-tetraketo- β -carotene was established by Karrer.

Crocetin, $C_{20}H_{24}O_4$, m.p. 285° , is present in the red colouring matter of saffron as the glycoside *crocin* (crocetin digentiobioside). It is a dicarboxylic acid with seven double bonds, which is represented by the symmetrical formula, $\text{HOOC} \cdot \text{CMe} : \text{A} : \text{CMe} \cdot \text{COOH}$ (for A see p. 831). Crocin has been shown to play an important part in the fertilisation of certain plants.

Bixin, $C_{25}H_{30}O_4$, m.p. 196° , is the yellow pigment of annatto seeds (*Bixa orellana*). It is formulated as $\text{HOOC} \cdot \text{CH} : \text{CH} \cdot \text{CMe} : \text{A} \cdot \text{CMe} \cdot \text{CH} : \text{CH} \cdot \text{COOMe}$. On ozonisation it yields β -acetylacrylic ester, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH} : \text{CH} \cdot \text{COOMe}$. Oxidation gives four molecular proportions of acetic acid, hence there are four methyl groups linked to the polyene chain. Bixin was formerly used for dyeing, and is still employed for colouring foodstuffs (butter, margarine) and in the manufacture of varnishes.

¹ L. Zechmeister and L. Cholnoky, *Ann.*, 1936, 523, 101.

ANTHOCYANINS¹

In this group are included the colouring matters of flowers and berries, which give rise to the wonderful variety of tints encountered in the vegetable kingdom.

The extracts from flowers, like the crude chlorophyll solutions obtained from leaves, contain the colouring matters admixed with highly complex substances of a colloidal nature, which render the isolation of the somewhat unstable pigments a difficult problem. Anthocyanins, however, although containing nitrogen in only a few cases, possess well-marked basic properties by means of which it is possible to effect their purification. They combine with mineral and organic acids to give well-defined crystalline salts. These salts are of the oxonium type, but they are less completely hydrolysed in solution than the salts of pyrones (p. 707). Anthocyanins are also phenolic in character and thus form salts with bases.

The compounds of anthocyanins with acids are red in colour, free anthocyanins are violet, and the alkali salts are blue. Many of the variations in the colours of flowers are due to the occurrence of anthocyanins in these three states. In addition, further changes in tint may arise from variations in the concentration of the anthocyanins and of other co-pigments in the plant tissues, such as tannins and flavonols. The colour of anthocyanins fades in solution as the result of structural changes. Many attempts were made to isolate the pure pigments, but success was only achieved in 1913 when Willstätter and Everest isolated the colouring material of the corn-flower. The correct anthocyanin formula was first advanced independently by Everest and Willstätter. Our knowledge of the anthocyanins is largely due to the pioneer work of Willstätter and the subsequent synthetic work of Robinson.

The anthocyanins are glycosides which are rapidly and completely hydrolysed by 20 per cent. hydrochloric acid into a sugar and the coloured aglycones known as anthocyanidins.

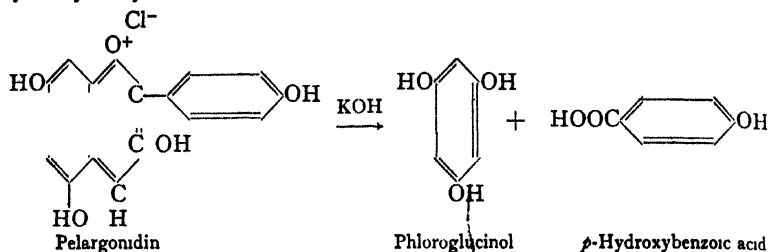
Constitution of the Anthocyanidins

The empirical composition of the sugar-free anthocyanidins suggests that they are closely allied to the yellow mordant colouring matters so widely distributed in plants, and especially to the dye-stuffs of the flavone and flavonol series, the structure of which has been established by the analytical investigations of A. G. Perkin and others, and the syntheses of Kostanecki (see p. 546). Thus cyanidin in its neutral state is isomeric with luteolin and kampherol: pelargonidin is isomeric with apigenin and galangin: and delphinidin with quercetin and morin.

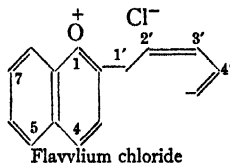
It would thus appear that the anthocyanidins are hydroxylated derivatives of 2-phenylbenzopyran and evidence was advanced to show that three of the hydroxyl groups are situated in the 3-, 5-, and 7'-positions and one or more in the phenyl side-chain. Pelargonidin chloride, for

¹ See *The Natural Organic Colouring Matters*, by A. G. Perkin and A. E. Everest (Longmans, Green & Co.), Hill, *Chem. Rev.*, 1936, 19, 27.

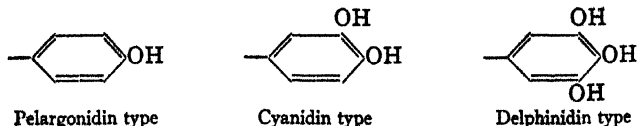
example, contains four hydroxy groups in the 3-, 5-, 7-, and 4'-positions (see formula given below). Now earlier work by H. Decker, W. H. Perkin, Jr., and R. Robinson had shown that stable oxonium salts known as 2-phenylbenzopyrylium or **flavylium salts** can exist and this led to the recognition that the anthocyanidins are hydroxy-flavylium salts. This is exemplified by pelargonidin chloride which is 3:5:7:4'-tetrahydroxy-flavylium chloride.



This formulation has been confirmed both by degradation and synthesis. Of importance in the former category is the fusion with sodium or potassium hydroxide which disrupts the molecule and yields two aromatic products, one of which is a phenol and the other a carboxylic acid. Pelargonidin chloride thus affords phloroglucinol and *p*-hydroxybenzoic acid. The anthocyanidins in this way resemble the flavone derivatives and the method is of great value in establishing their structures. A

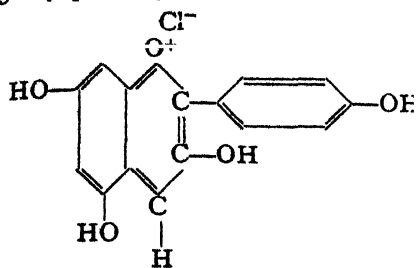


systematic application of this and other methods to the anthocyanidins shows that they all yield phloroglucinol (or its mono-methyl ether) on the one hand and *p*-hydroxy-benzoic acid, 3:4-dihydroxy-benzoic acid (protocatechuic acid), or 3:4:5-trihydroxy-benzoic acid (gallic acid) or their methylated derivatives on the other. There are thus three fundamental types of anthocyanidins, which differ in the number of hydroxyl groups in the phenyl ring, as shown in the formulæ for pelargonidin, cyanidin, and delphinidin chloride respectively.

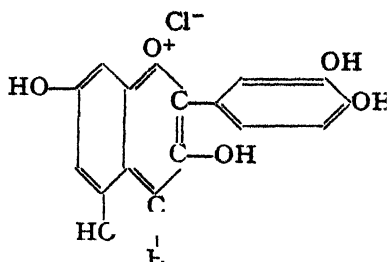


All other anthocyanidins are methylated or acylated derivatives of one or other of these parent compounds, the most important being the mono-, di-, and tri-methyl ethers, **peonidin**, **malvidin** (*syringidin*), and **hirsutidin chloride**. The systematic nomenclature of these compounds is based

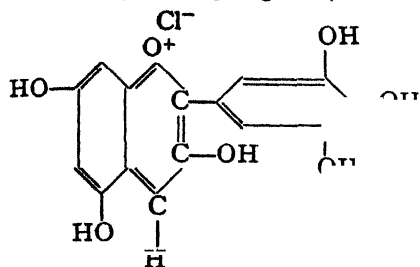
on the numbering given above, according to which cyanidin is 3 : 5 : 7 : 3' : 4'-pentahydroxyflavylium chloride



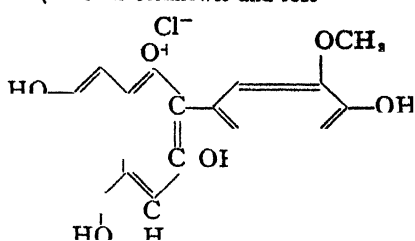
Pelargonidin chloride
(from the pelargonium)



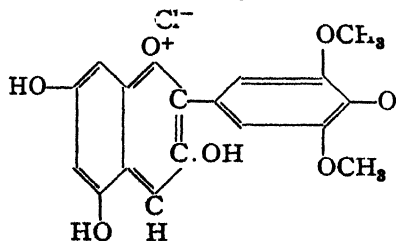
Cyanidin chloride
(from the cornflower and rose)



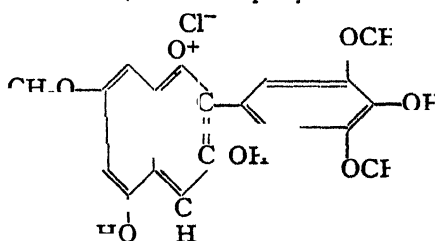
Delphinidin chloride
(from the delphinium)



Peonidin chloride
(from the red peony)



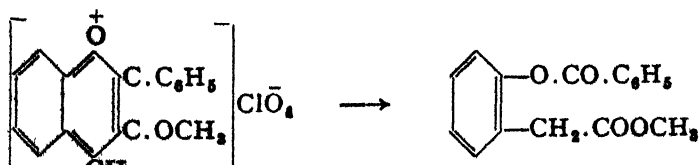
Malvidin (syringidin) chloride
(from wild mallow and grape)



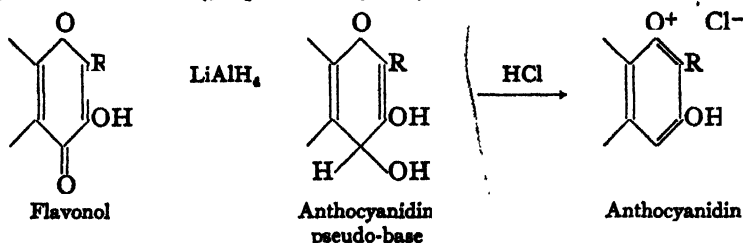
Hirsutidin chloride
(from *Primula hirsuta*)

These methylated anthocyanidins are best degraded by Karrer's method using hot dilute (10 per cent.) alkali in an atmosphere of hydrogen, thus avoiding demethylation which occurs with concentrated alkali.

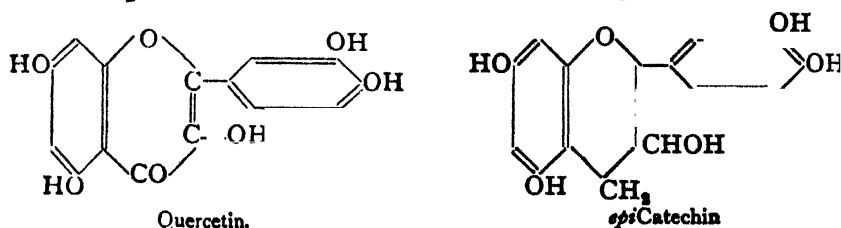
The constitution of the heterocyclic ring in the anthocyanidins and other flavylium salts has been confirmed by other evidence. Diltley, for example, oxidised 3-methoxyflavylium perchlorate with an acetic acid solution of hydrogen peroxide which led to the rupture of the 2 : 3-double bond and the formation of the benzoyl derivative of methyl *o*-hydroxy-naphthalacetate.



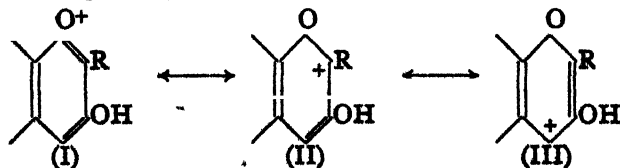
Convincing evidence is also provided by the reduction of anthocyanidins and related compounds. The formula assigned to cyanidin chloride suggests that this compound could be prepared from quercetin and that anthocyanidins in general could be obtained by the reduction of the corresponding flavonols. This is readily seen by comparing the above formula for cyanidin chloride with the following one for quercetin. By reducing quercetin with magnesium and aqueous methanolic hydrogen chloride, Willstätter and Mallison did succeed in isolating a small quantity of cyanidin. Recently it has been found that reduction of quercetin with lithium aluminium hydride gives a much better yield of cyanidin chloride (28 per cent.), while kaempferol by the same method gives pelargonidin chloride (32 per cent. yield).¹



It is also to be anticipated that reduction of cyanidin chloride will yield catechin or *epicatechin* and this has been realised experimentally.



In the formulæ given above the anthocyanidins have an oxonium salt structure with a positive charge on the oxygen atom. There is evidence, however, that the anthocyanidin cation has a resonating structure with contributing forms (I, II and III) containing the positive charge on the oxygen, C_2 or C_4 atoms.



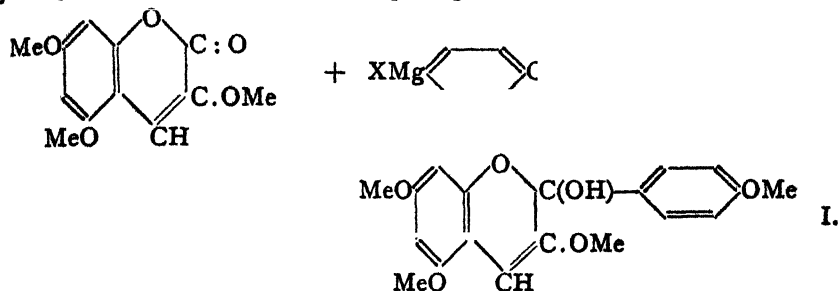
In support of the carbonium ion structures (II and III) it has been found that flavylum ions undergo chemical attack at C_2 and C_4 , and further undergo oxidative ring-fission both at the C_2 - C_3 and C_3 - C_4 bonds.²

Syntheses of Anthocyanidins and Anthocyanins.—One method is to

¹ R. Robinson and R. Mirza, *Nature*, 1950, 166, 997.

² D. Hill, *Chem. Rev.*, 1936, 19, 27.

treat coumarins with aryl magnesium halides. For example, by interaction of 3:5:7-trimethoxy-coumarin and anisyl magnesium halide Willstätter prepared the carbinol base I. On being heated in a sealed tube with concentrated hydrochloric acid the methoxy groups were hydrolysed with the formation of pelargonidin chloride.¹

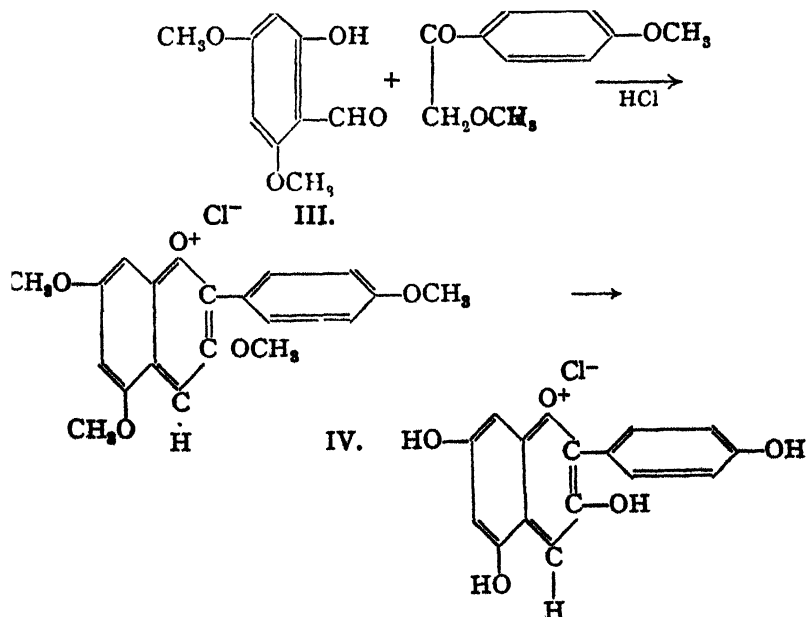


A more general method is to start from substituted *o*-hydroxy-benzaldehydes and acetophenones as illustrated in the following synthesis of pelargonidin by Robinson and Pratt.

2-Hydroxy-4:6-dimethoxy-benzaldehyde (I) and *o*:4-dimethoxy-acetophenone (II) were condensed together in ethereal solution, in the presence of dry hydrochloric acid gas, to give tetramethyl-pelargonidin chloride (III). The latter was then demethylated to pelargonidin

I.

II.

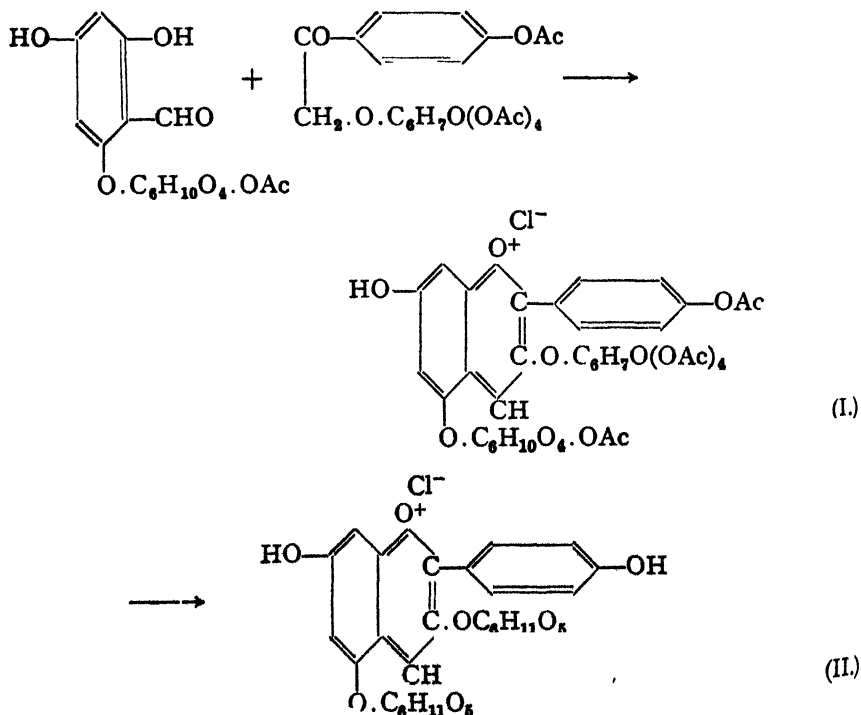


¹ An extended examination of this reaction by Heilbron (see Heilbron, D. Hill and Walls, *J.*, 1931, 1701) showed that the formation of flavylum salts depends greatly on the experimental conditions and on the nature and position of substituents. 4-Substituted coumarins only give very small yields, the main product being a diaryl- Δ^8 -chromene.

chloride (IV) by boiling with hydriodic acid in the presence of phenol. Purer products are usually obtained by protecting the hydroxyl groups by acetylation or benzylation.

On applying similar methods to substances containing sugar residues, Robinson¹ succeeded in synthesising a number of the naturally occurring anthocyanins in such a manner as to establish their structures. Thus pelargonin was obtained by condensing the *o*-acetylglucosidyl derivative of phloroglucinaldehyde with ω -*o*-tetracetyl- β -glucosidyl-4-acetoxyacetophenone (prepared from acetbromoglucose, ω -hydroxy-4-acetoxyacetophenone and dry silver carbonate in benzene) with the aid of hydrogen chloride in dry ethyl acetate. The intermediate flavylum salt I, which was first formed, was allowed to stand in contact with dilute alkali in an atmosphere of hydrogen, when the protective acetyl groups were hydrolysed off. Final acidification with hydrochloric acid yielded pelargonin chloride II.

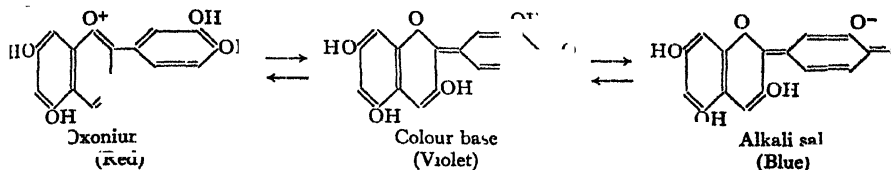
These investigations have shown that the carbohydrate is commonly united to position 3, or positions 3 and 5, of the anthocyanidin nucleus, and that the majority of these compounds may be classified as belonging to one or other of the following groups: (a) 3-monoglucosides and 3-monogalactosides, (b) 3-rhamnosides and other 3-pentoseglycosides, (c) 3-biosides, (d) 3:5-diglycosides and (e) acylated anthocyanins.



¹ A. Robertson and Robinson, *J.*, 1928, 1256; Robinson and A. R. Todd, *ibid.*, 1932, 2293, 2299, 2488. Robinson and Robinson, *Nature*, 1933, 132, 625.

The best known and most widely occurring anthocyanins are those of group (d), which includes *pelargonin*, the 3:5-diglucoside of pelargonidin, and *cyanin*, the 3:5-diglucoside of cyanidin. Among the acylated derivatives of group (e) are *delphinin*, a *p*-hydroxybenzoylated monoglucoside of delphinidin, and *gentianin*, the corresponding *p*-hydroxycinnamoyl derivative. Further information regarding these compounds has already been given in the earlier part of this section.

Colour Changes of the Anthocyanidins.—The colour of the anthocyanidins varies with the pH of the solution. Thus cyanidin at pH 3 or less is red; at pH 8.5 violet; and at pH 12 blue. These colour changes are the result of structural changes of the anthocyanidin molecule. The red colour is attributed to the oxonium (or carbonium) ion, which with alkali yields the violet colour base. Further addition of alkali gives the pure blue alkali salt.



Anthocyanins and Anthocyanidins—The first anthocyanin to be obtained in the form of its crystalline chloride was *cyanin*, the pigment of the corn-flower.¹ In the blue flower it is present as the potassium salt.

The colouring matter of the red rose has also proved to be identical with cyanin. For preparative purposes the rose is a better starting material than the cornflower. From the dried petals it is possible to obtain approximately 1 per cent. of their weight as the crystalline cyanin chloride.

On hydrolysis cyanin decomposes into *cyanidin* and two molecules of glucose.

Cyanidin has the composition $C_{15}H_{10}O_6$, and its chloride, $C_{15}H_{11}O_6Cl$.

The anthocyanin *pelargonin* present in the scarlet pelargonium is a diglucoside of the anthocyanidin *pelargonidin*, $C_{15}H_{10}O_5$, which contains one oxygen atom less than cyanidin.

The violet flowers of the delphinium (*Delphinium consolida*) contain the anthocyanin *delphinin*, which is of more complex structure. On hydrolysis it decomposes into two molecules of glucose, two molecules of *p*-hydroxybenzoic acid and one molecule of anthocyanidin. The latter, which has been named *delphinidin*, gives a chloride of the formula $C_{15}H_{11}O_6Cl$, and thus contains one atom of oxygen more than cyanidin.

Cenin, the colouring matter of the blue grape, and *malvin*, present in the wild mallow, are mono- and di-glucosides respectively of *malvidin*. On being warmed with hydriodic acid malvidin loses two methyl groups and is converted into delphinidin, of which it is therefore a dimethyl ether.

¹ Willstätter and Everest, *Ann.*, 1913, 402, 189.

Peonin is a diglucoside of **peonidin** and is the colouring matter of the red peony. **Hirsutin**, from *Primula hirsuta*, is a diglucoside of **hirsutidin**, containing three methyl ether groupings. **Chrysanthemin** or **asterin** is a monoglucoside of cyanin present in the scarlet aster.

XI

Vitamins, Hormones, and Enzymes

Vitamins and *hormones* are organic compounds of extraordinarily high physiological potency which are essential in small amounts for the well-being of all animal organisms. The distinction between the two groups is not always very clearly marked, but in general the term vitamin is used to describe principles which are already present in the active state in foodstuffs, whereas the name hormone is reserved for those which are elaborated within the organism by special glands or tissues, such as the thyroid and pituitary glands.

VITAMINS¹

Until the beginning of the century it was assumed that minerals, fats, carbohydrates, and proteins are sufficient to ensure growth and health in animals. More detailed investigations showed, however, that other organic compounds are required and these were called vitamins. They are characterised by their extraordinarily high physiological potency and are required only in small amounts for the well-being of all animal organisms. Many vitamins are supplied by foodstuffs, but some, such as various members of the vitamin B complex, can be synthesised in certain animals by bacteria.

Recently there has been considerable discussion about the definition of a vitamin and there is no general agreement whether compounds such as choline should be classified as vitamins.² The problem has not been simplified by the discovery that micro-organisms require minute quantities of growth factors for their development. Doubtless a precise definition will be given in the near future.

In this chapter only those vitamins are mentioned whose molecular constitutions have been at least partially established. The vitamins designated briefly by the letters A, B, C, D, E, and K have been examined in considerable detail.

There are a number of compounds related to the vitamins known as *provitamins* which have no biological activity but are transformed by simple processes into vitamins. An example of a provitamin is *hitol*, a dihydric alcohol, $C_{40}H_{60}O_2$, which occurs in whale liver oil.³ It is converted into vitamin A when heated above 200° and is therefore a provitamin A. Other examples of provitamins will be found on next page

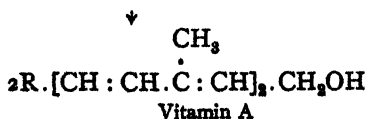
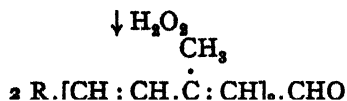
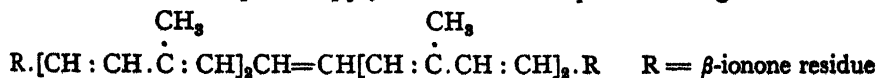
¹ *Chemistry and Physiology of the Vitamins*, H. R. Rosenberg (1942). ² F. A. Robinson and others, *Chem. and Ind.*, 1944, 45, 388. ³ Embree and Schanz, *J.A.C.S.*, 1943, 65, 910.

In the following list are given the vitamins whose chemical structures

Vitamins of known Chemical Constitution

Vitamin A or A ₁	Axerophthol
Vitamin A ₂	
Vitamin B ₁	Thiamin
Vitamin B ₂	Riboflavin
Vitamin B ₆	Pyridoxin
Vitamin B ₁₂	Cyanocobalamin
Folic acid	
Nicotinic acid or amide	Vitamin B Complex
Pantothenic acid	
Inositol	
<i>p</i> -Aminobenzoic acid	
Vitamin C	Ascorbic acid
Vitamin D ₂	Ergocalciferol
Vitamin D ₃	Cholecalciferol
Vitamin D ₄	
Vitamin D ₅	
Vitamins E	
α -Tocopherol	
β -Tocopherol	
γ -Tocopherol	
δ -Tocopherol	
Vitamin K ₁ , K ₂ , K ₃ , K ₄ , K ₅	

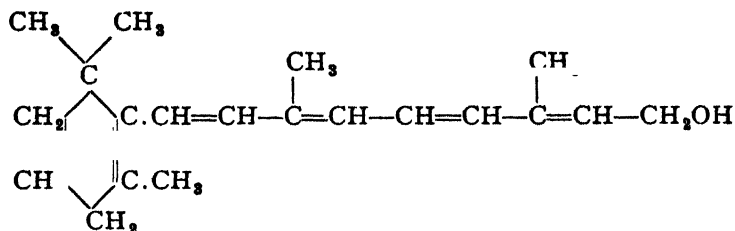
Vitamin A (*axerophthol*), a "fat-soluble" vitamin, is found in association with fats and is present in high concentration in the liver oils of fishes such as cod and especially halibut. It was originally discovered and studied in cod-liver oil, where it occurs in conjunction with vitamin D, another fat-soluble compound. Vitamin A promotes the growth of young animals and an adequate supply of it serves as a protection against certain



types of infection. One of the earliest signs of vitamin A deficiency is night blindness; a continued lack of the vitamin may lead to hardening of the conjunctiva, corneal softening (*xerophthalmia*) and to complete blindness. Structurally, the vitamin is closely related to the carotenes of plants present in carrots and green vegetables, which can also serve as a source of the compound. In this case the provitamin or immediate

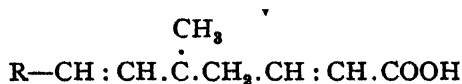
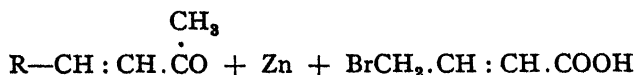
precursor of the active principle is the intensely yellow polyene hydrocarbon *carotene*, $C_{40}H_{56}$ (see p. 830), which is converted into vitamin A in the liver. This relationship was shown by the oxidation of β -carotene by hydrogen peroxide in glacial acetic acid to vitamin-A aldehyde and subsequent reduction with aluminium isopropoxide or lithium aluminium hydride to vitamin A.¹ There are a number of other provitamins A such as *cryptoxanthin*, *myxoxanthin*, and other carotenoids.

The molecular structure of vitamin A was established by the work of Karrer and of Heilbron. It is a crystalline compound, m.p. $63-64^{\circ}$.²

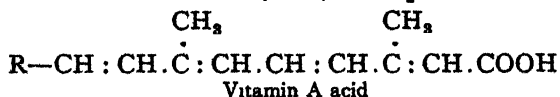
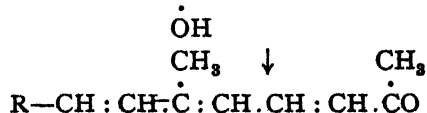


with the annexed structure, representing a highly unsaturated alcohol built up from four isoprene units and containing a β -ionone ring.

Vitamin A on catalytic hydrogenation absorbs five molecules of hydrogen to give perhydro-vitamin A, $C_{40}H_{40}O$, which has been synthesised. The synthesis of the vitamin, difficult on account of the fragile side-chain, was, after intensive research, successfully accomplished. As an example of the methods used the synthesis of vitamin-A acid, which has pronounced vitamin-A properties, may be mentioned. The synthesis starts from a β -ionone derivative which has been used for nearly all the attempted syntheses. As will be seen from the equations, the Reformatsky reaction is twice used, and, it is interesting to note, one of the essential reactants, 3-bromocrotonic acid, formerly a rare chemical,



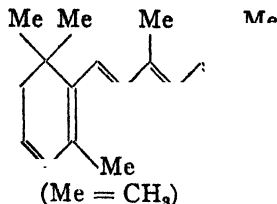
R = β -ionone residue



¹ R. F. Hunter and N. E. Williams, *J.*, 1945, 554. N. L. Wendler, C. Rosenblum and M. Tishler, *J.A.C.S.*, 1950, 72, 234. ² J. G. Baxter and C. D. Robeson, *J.A.C.S.*, 1942, 64, 241.

is now available as the result of recent work on the participation of free radicals in halogenation (see p. 140).

The presence of a second vitamin A in fresh-water fish liver oils was first indicated by the ultra-violet measurements of Heilbron, Morton, and their co-workers. While vitamin A absorbs mainly at 328 $m\mu$, the new vitamin (vitamin A₂) absorbs at 351 $m\mu$. The formula of vitamin A₂ has been proved to be:¹

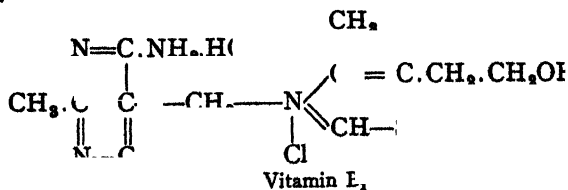


Vitamin B Group.²—A number of vitamins occurring together in yeast, etc., was first thought to be a single compound—vitamin B. Research showed that there were present a number of components and the mixture was rather unfortunately termed the vitamin B complex. A more appropriate name is the vitamin B group. It contains the following vitamins: vitamins B₁, B₂, B₆, B₁₂, biotin, nicotinic acid, pantothenic acid, inositol, *p*-aminobenzoic acid, and folic acid.

The members of this group are present in liver, yeast, milk, and vegetables and have the common property of stimulating the growth of various micro-organisms. They are all water-soluble.

Vitamin B₁, aneurin, thiamin, is a thermolabile compound which is essential for the normal progress of carbohydrate metabolism. When deficiency occurs pyruvic acid and other ketonic compounds accumulate in the organism instead of undergoing further degradation, with results that may lead to beri-beri and neuritis. The antineuritic vitamin is widely distributed in natural foods, being present in the cortical parts of grain, but not in the endosperm; it is relatively abundant in yeast, where it is accompanied by other members of the B group. Cases of beri-beri among natives living on rice have been traced to loss of aneurin due to the outer surface of the grain having been removed by friction during transit. The powdery "rice-polishings" constituting this part of the grain have served as a source of the vitamin.

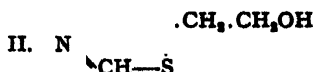
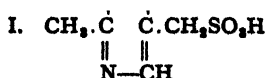
Aneurin has the empirical formula C₁₂H₁₈ON₄Cl₂S. Its structure is as follows:



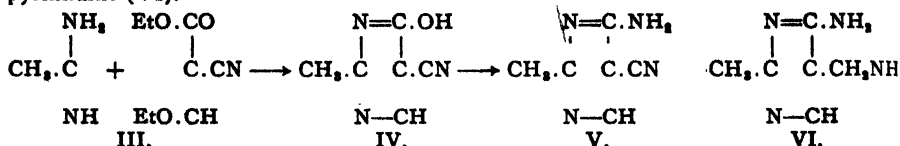
¹ K. R. Farrar, J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J.*, 1952, 265.

² For survey, see R. D. Haworth, *Ann. Reports*, 1937, 34, 352. A. R. Todd, *J.*, 1941, 42. F. A. Robinson, *Chem. Ind.*, 1944, 22, 270, 286.

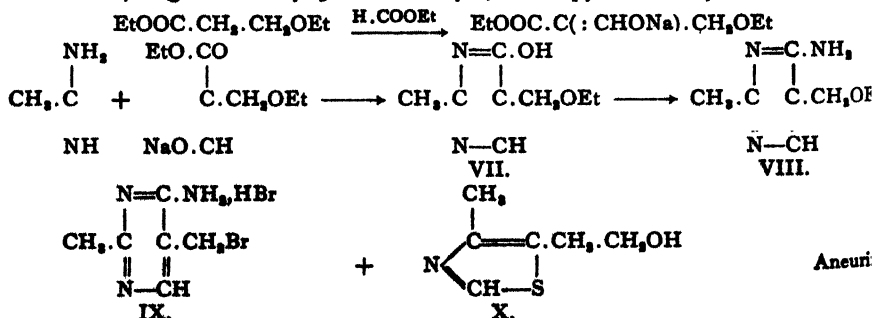
The determination of the structure was mainly due to R. R. Williams, who observed that aneurin was quantitatively disrupted by aqueous sodium bisulphite into two components. One, a base, was found to be oxidisable to the known 4-methylthiazole-5-carboxylic acid and was formulated as 4-methyl-5-hydroxyethyl-thiazole (II), later confirmed by synthesis.¹ Examination of the other component proved it to be a sulphonic acid derived from 4-amino-2-methyl-pyrimidine (I). The key to the exact structure of the pyrimidine fragment in aneurin was found in a diacidic base obtained from the vitamin by use of alkaline permanganate or of sodium in liquid ammonia. This was shown to be 4-amino-5-aminomethyl-2-methyl-pyrimidine (VI) by its synthesis from



acetamidine by several workers.² Todd and Bergel obtained it by condensing acetamidine with ethyl α -ethoxymethylene- α -cyanoacetate (III) to form an intermediate compound which on being heated with alkali gave 4-hydroxy-5-cyano-2-methyl-pyrimidine (IV). This last compound was refluxed with phosphoryl chloride ($\text{OH} \rightarrow \text{Cl}$) and treated with ammonia ($\text{Cl} \rightarrow \text{NH}_2$), yielding 4-amino-5-cyano-2-methyl-pyrimidine V, which on catalytic reduction was converted in 4-amino-5-aminomethyl-2-methyl-pyrimidine (VI).



These preliminary investigations were rapidly followed by several syntheses of aneurin itself,³ those of Williams in America and Grewe in Germany being on very similar lines. Williams's method, which has been used on a large scale, is as follows: β -ethoxy-propionic ester reacts with ethyl formate in the presence of sodium ethoxide to give ethyl sodioformyl- β -ethoxy propionate, which is condensed with acetamidine to form 2-methyl-5-ethoxymethyl-4-hydroxy-pyrimidine (VII). The hydroxyl group in the latter is replaced successively by Cl and NH_2 by use of phosphorus oxychloride followed by ammonia, and the resulting compound (VIII) heated with hydrogen bromide ($\text{OEt} \rightarrow \text{Br}$) to give 2-methyl-5-bromomethyl-4-amino-pyrimidine hydrobromide (IX).

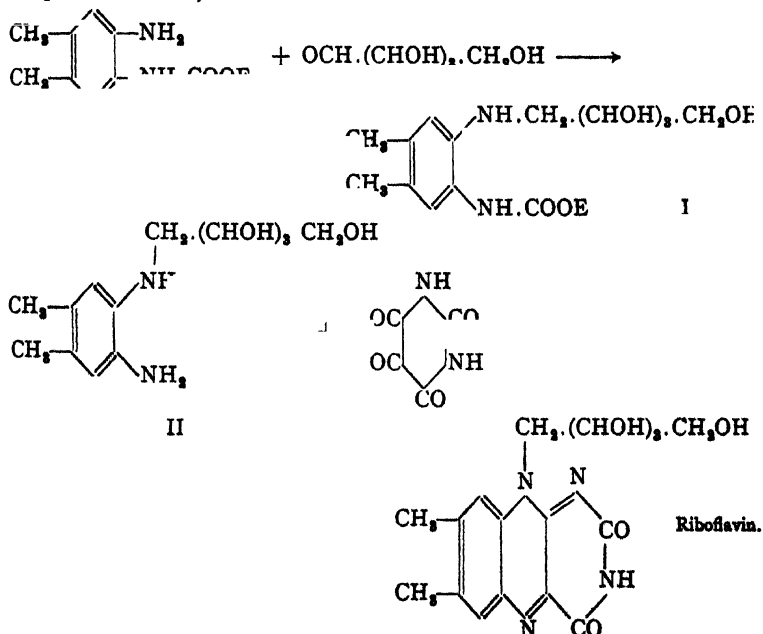


In the final stage the bromocompound IX is heated for a short time with 4-methyl- β -hydroxyethyl-thiazole (X, see above) to form the hydrobromide of vitamin B₁ in good yield. When converted into the hydrochloride the synthetic vitamin had the same physiological activity as the natural product.

¹ H. T. Clarke and S. Gurin, *J.A.C.S.* 1935, 57, 1876. ² A. R. Todd and F. Bergel, *J.* 1937, 354; R. Grewe, *Z. physiol. Ch.*, 1936, 222, 89; Andersag and Westphal, *Ber.*, 1937, 70, 2035. ³ Cline, Williams and Finkelstein, *J.A.C.S.*, 1937, 59, 1052; Todd and Bergel, *J.*, 1937, 1504; Andersag and Westphal, *loc. cit.*

The pyrophosphoric ester of aneurin is the co-enzyme of carboxylase which is essential for the breakdown of pyruvic acid in the body, and which also takes part in alcoholic fermentation.

Vitamin B₂, riboflavin, lactoflavin, is a growth-promoting factor which remains with the other thermostable members of the B group after vitamin B₁ has been destroyed by heating in an autoclave. It was discovered mainly through the work of Kuhn, György and Wagner-Jauregg on a yellow pigment obtained from whey, which was identified with vitamin B₂. The structure of this compound, riboflavin, was established by the researches of Kuhn and of Karrer. The latter effected the first complete synthesis, starting from an equimolecular mixture of 1-amino-2-carbethoxyamino-4 : 5-dimethylbenzene and D-ribose, which was hydrogenated in the presence of nickel to form 2-carbethoxyamino-4 : 5-dimethyl-phenylribamine (I). This compound was hydrolysed by alkali to 2-amino-4 : 5-dimethyl-phenylribamine (II), followed by condensation with alloxan in acid solution. The resulting 6 : 7-dimethyl-9-D-ribityl-isalloxazin, was identical with riboflavin.



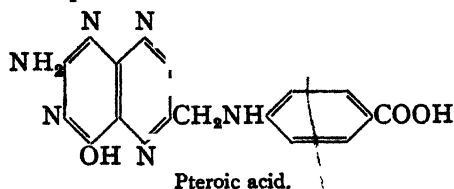
Riboflavin is a yellow crystalline compound, m.p. 298°, which is soluble in water to a yellow-green fluorescent solution. Among the best sources are yeast, vegetables, milk and liver. The phosphoric ester of riboflavin, esterified in position 5 of the ribose group, is present in Warburg's yellow respiration enzyme, and has been prepared from riboflavin.

Folic Acid Vitamins.—Folic acid was the name given by Mitchell, Snell and Williams to a growth factor for *Streptococcus lactis* R., obtained

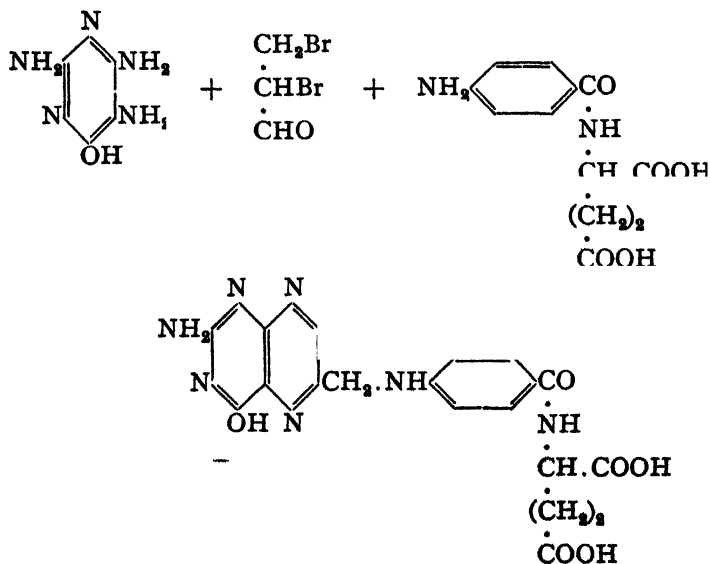
from spinach leaves, but has since been applied without chemical definition to a number of substances which stimulate bacterial growth. Considerable confusion has as a result arisen. It is now generally applied to a series of derivatives of pteronic acid (see below) which play a part in the prevention of anæmia. Among these substances are :

N-Pteroyl-glutamic acid
 Pteroyldi-glutamylglutamic acid
 Pteroylhexa-glutamylglutamic acid

When the term folic acid is applied to a single substance it refers to the first of these compounds.



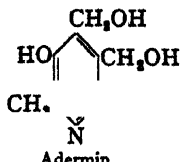
Pteroylglutamic acid is a bright yellow crystalline substance, built up from *p*-aminobenzoic acid, L-glutamic acid, and 2-amino-6-hydroxy-8-methyl-pteridine. It has been synthesised, one method involving the interaction of 2:4:5-triamino-6-hydroxypyrimidine, *p*-aminobenzoyl-L-glutamic acid, and α : β -dibromopropionaldehyde in the presence of an acetate buffer.



It is used clinically for pernicious anæmia, though inferior in some respect to liver extract. It is not yet decided if it is identical with the folic acid from spinach.

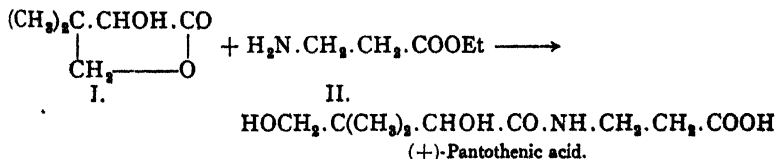
Nicotinic acid is the anti-pellagra ¹ vitamin. It has been isolated from yeast and rice, where it is accompanied by other members of the B complex, and also in the form of nicotinamide from heart, muscle and liver.

Vitamin B₆, adermin, pyridoxin, has been found to be specific against rat dermatitis. Researches carried out in the Merck laboratories ² in America and by R. Kuhn in Germany have shown it to be a relatively simple derivative of pyridine, namely 2-methyl-3-hydroxy-4:5-di-(hydroxymethyl)-pyridine. The vitamin was isolated from rice bran as the hydrochloride of a weak tertiary base, C₈H₁₁O₃N, which was found to contain one C-methyl group, one phenol group (methylated by diazomethane) and two primary alcohol groups. The absorption spectrum classed it as a 3-hydroxy-pyridine. Oxidation with alkaline permanganate converted the methylated vitamin into a methoxy-picoline dicarboxylic



acid I, the absorption spectrum of which strongly resembled that of 2:6-dimethylcinchoneric acid. The acid also gave the fluorescein reaction, and was therefore concluded to have the carboxyls in adjacent positions. Decarboxylation with lime converted the acid into a hydroxypicoline, the picrate of which melted at 147° to 148° and was thus not that of 3-hydroxy-6-methyl pyridine, whose picrate melts at 201° to 202°, but presumably of the isomeric 2-methyl derivative. Finally, the vitamin in alkaline solution gave a blue colour with 2:6-dichloro-quinone-chloroimide, indicating that the para position to the phenolic group is unsubstituted.³ In this way the above formula was deduced, and was later confirmed by synthesis.^{4 5}

Pantothenic Acid.—In 1933 R. J. Williams found that extracts from a very wide range of biological tissues contained a material having a remarkable stimulating effect on the growth of yeast. The active principle



was later isolated from liver and was termed pantothenic acid (*Greek*: from everywhere). Further examination showed it to be identical with the "chick-dermatitis factor" and to be of importance in animal nutrition.

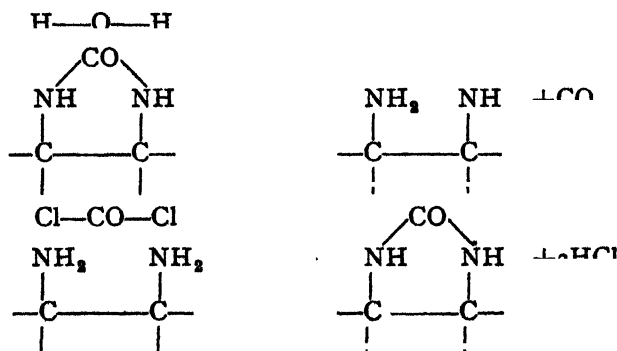
¹ Pellagra is a disease involving serious skin lesions. ² E. T. Stiller, Keresztesy and Stevens, *J.A.C.S.*, 1939, 61, 1237; S. A. Harris, Stiller and K. Folkers, *ibid.*, p. 1242; Harris and Folkers, *ibid.*, p. 1245. ³ Gibbs, *J. Biol. Chem.*, 1927, 72, 649; see also Theriault, *Ind. Eng. Chem.*, 1929, 21, 343. ⁴ E. T. Stiller, Keresztesy and Stevens, *J.A.C.S.*, 1939, 61, 1237; S. A. Harris, Stiller and K. Folkers, *ibid.*, p. 1242; Harris and Folkers, *ibid.*, p. 1245. ⁵ Kuhn and co-workers, *Ber.*, 1939, 66, 205, 206, 210.

As the result of brilliant micro-chemical investigations,¹ the vitamin has been characterised as *N*-(α -dihydroxy- β - β -dimethyl-butyryl)- β -aminopropionic acid. This structure was confirmed by a synthesis, based on the condensation at 70° of its component parts, (—)- α -hydroxy- β - β -dimethyl- γ -butyrolactone (I) and the ethyl ester of β -alanine (II), followed by removal of the ethyl groups by use of cold baryta.

Biotin, $C_{10}H_{16}O_3NS$, is an essential growth factor both for yeasts and the nitrogen-fixing bacterium *Rhizobium* and has, in addition, the remarkable property of preventing "egg white injury" in rats fed on raw egg white. The chemical structure of biotin has been determined as the result of the work of a number of investigators including Kög (Utrecht) and particularly du Vigneaud² (Cornell University, U.S.A.). It has been synthesised by a group in the Merck laboratories (U.S.A.).

Some idea of the difficulties encountered by workers on biotin may be obtained from the fact that Kög worked up 250 kilos of dried egg yolk to obtain 1.1 mg. of the crystalline vitamin.

β -Biotin was obtained by the American workers from liver and mill in the form of long thin needles, m.p. 230-232°. It is optically active, dissolves in sodium hydroxide, and forms a methyl ester with ease. The titration curve resembles that of a monocarboxylic acid. Two of the three oxygen atoms therefore are accounted for. The remaining oxygen and the two nitrogen atoms were shown to form part of a cyclic urea ring since vigorous hydrolysis with barium hydroxide (20 hours at 140° C.) gave a diamino-acid, a carbon and an oxygen atom being lost in the process. Regeneration of the vitamin was effected by the action of phosgene on the diamino-compound.



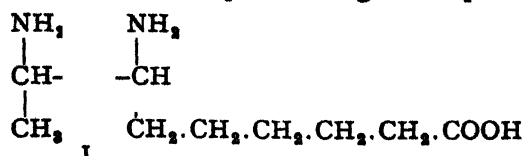
Since the diamino-compound forms a quinoxaline with phenanthraquinone the amino-groups must lie on contiguous carbon atoms and the cyclic urea ring must therefore be five-membered.

Oxidation with hydrogen peroxide converted the sulphur into a sulphone group thus showing the presence of a thioether linkage, $C-S-C$.

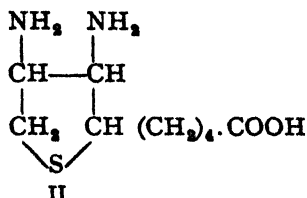
¹ See R. J. Williams and R. T. Major, *Science*, 1940, 91, 246; E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy and K. Folkers, *J.A.C.S.*, 1940, 62, 1785; R. J. Williams, H. K. Mitchell, H. H. Weinstock and E. E. Snell, *ibid.*, p. 1784. ² V. du Vigneaud, *Science*, 1942, 96, 455; Openshaw, *Ann. Reports*, 1943, 40, 172.

Removal of the sulphur by treatment with Raney nickel resulted in fission of one of the rings but not in disruption of the molecule, two hydrogen atoms being added in the process. The sulphur must therefore be part of a ring system.

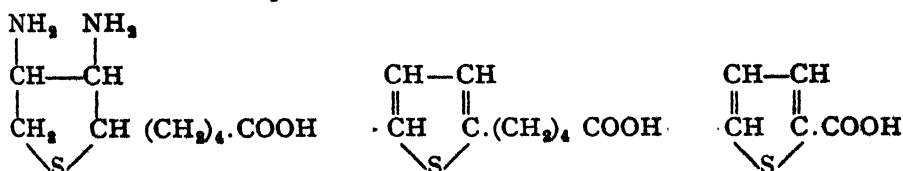
The presence of a second five-membered ring was deduced from a number of observations. The compound obtained by the removal of sulphur was hydrolysed to a diamino-compound which was shown to have formula I. Further oxidation experiments gave adipic acid which was



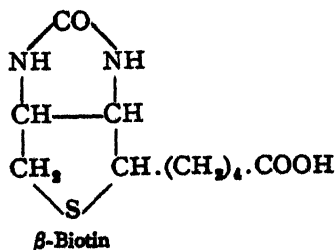
shown to be obtained from a valeric acid side-chain. The diamino-compound obtained by rupture of the cyclo urea ring must therefore have a formula such as II



Formula II was confirmed by its degradation by a modified Hofmann exhaustive methylation method to δ -(α -thienyl)-valeric acid which in turn was oxidised to α -thiophenic acid.



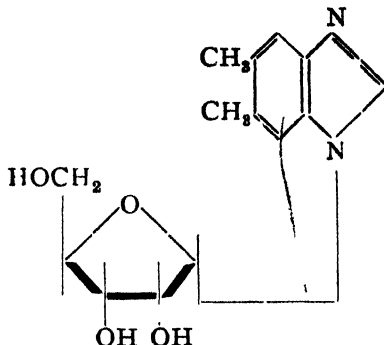
These and other results indicate that biotin has the annexed formula and this has been confirmed by synthesis.¹ The synthetic DL-biotin was resolved and the D-biotin found to be identical with β -biotin from liver extract.



¹ S. A. Harris, D. E. Wolf, R. Moxingo, K. Folkers, *Science*, 1943, 97, 447. S. A. Harris and co-workers, *J.A.C.S.*, 1944, 66, 1756.

Vitamin B₁₂ Group.—Vitamin B₁₂ is isolated from liver as a red crystalline compound, which like liver extracts is effective in the treatment of pernicious anæmia. Several other crystalline compounds with vitamin B₁₂ activity are known. All are essential for human growth.

The structure of vitamin B₁₂ has been only partially elucidated, but it has certain unusual structural features including a cobalt atom and cyano-groups. It contains 5 : 6-dimethylbenzimidazole linked to D-ribose since on hydrolysis it yields 1- α -D-ribofuranosido-5 : 6-dimethylbenzimidazole. It is also known that the ribose is phosphorylated.



1- α -D-Ribofuranosido-5 : 6-dimethylbenzimidazole

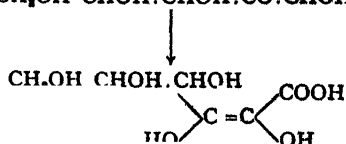
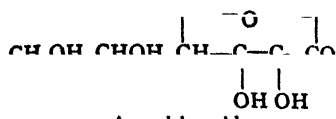
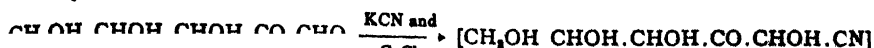
Vitamin C, L-Ascorbic Acid.—In 1928 a highly reactive crystalline acid, C₆H₈O₆, was isolated by A. Szent-Györgyi from a number of sources including adrenal cortex, cabbages and oranges. This compound possessed strong antiscorbutic properties and was subsequently named *ascorbic acid*. It was quickly realised that it might prove to be the hitherto unidentified vitamin C, a component of food which is essential for the prevention of scurvy. From the above materials ascorbic acid was only obtainable in small amounts, but Szent-Györgyi ¹ later discovered a very rich source in Hungarian pepper, from which considerable quantities could be extracted.

An investigation of ascorbic acid from the last source by Hirst and his co-workers ² showed it to be a simple derivative of the hexose L-gulose, possessing the constitution given on next page. This structure was brilliantly verified shortly afterwards by the synthesis carried out by Haworth, Hirst and a team of collaborators,³ the first synthesis of a vitamin to be achieved.

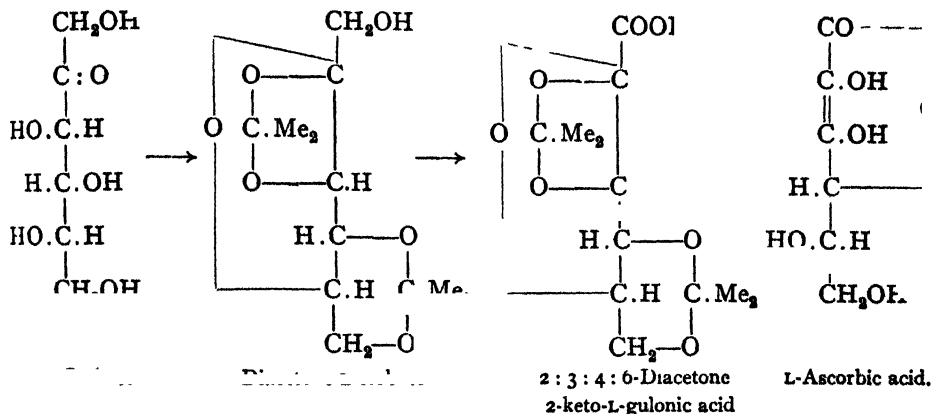
The starting point in the synthetic preparation was the previously unknown L-xylosone. This was first converted into the cyanhydrin, which almost immediately underwent hydrolysis to give the corresponding

¹ I. Banga and A. Szent-Györgyi, *Biochem. J.*, 1934, **28**, 1625. ² R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J.*, 1933, 1270. ³ W. N. Haworth and E. L. Hirst, *J.S.C.I.*, 1933, **52**, 645; R. G. Ault, D. K. Baird, H. C. Carrington, W. N. Haworth, R. Herbert, E. L. Hirst, E. G. V. Percival, F. Smith and M. Stacey, *J.*, 1933, 1419.

keto-acid (written below in its enolic form). The latter, in the presence of dilute hydrochloric acid was transformed quantitatively into L-ascorbic acid, identical with the natural vitamin. D-Ascorbic acid was also prepared from D-xylosone, but was found to display little or no physiological activity.



L-Ascorbic acid is now manufactured by condensing L-sorbose (from D-glucose) with acetone and sulphuric acid to give diacetone sorbose which is then oxidised to diacetone keto-L-gulonic acid. Finally treatment with gaseous hydrochloric acid gives L-ascorbic acid.



The accepted structure of ascorbic acid is in agreement with its chemical properties, provided the possibilities of the molecule to undergo keto-enolic change are borne in mind. The acid gives a quantitative yield of furfuraldehyde when boiled with hydrochloric acid ; it forms a diphenylhydrazone (ketonic structure) and gives an intense coloration with ferric chloride (enolic structure). Schiff's reagent produces no coloration, thus indicating the absence of a free aldehyde group. The most characteristic reaction, and one which is closely related to its biological activity, is the ease with which it undergoes reversible oxidation to *dehydroascorbic acid*, when the group $\text{C}(\text{OH}) = \text{C}(\text{OH})$ present in the ring is dehydrogenated to $\text{CO}-\text{CO}$. In this way Vitamin C is believed to regulate the oxidation-reduction processes of the living cell, aiding cellular respiration by acting as a hydrogen transporter. In addition to its anti-scorbutic activity the vitamin assists the body to withstand bacterial infection and toxins.

L-Ascorbic acid is contained in most fresh foods, and especially in fruit and green vegetables, in amounts which vary greatly with the species. As already stated it occurs in considerable proportions in Hungarian pepper. The compound is less stable than the other known vitamins, and is destroyed when the foods in question are heated, dried or even kept for long periods.

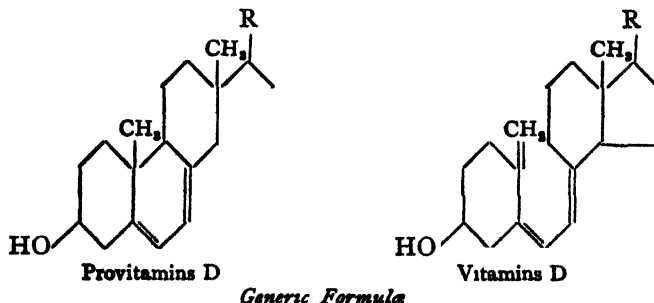
Vitamin D, which may exist naturally in more than one form, is a specific against rickets. It is essential for the absorption of phosphorus and calcium from the intestine and thus for maintaining the normal calcium and phosphorus levels in the body. It is present in high concentrations in fish-liver oils, the most potent being those from the percomorph family, *e.g.* mackerel. Halibut and cod-liver oils are used medicinally.

By vitamin D is meant a number of closely related compounds with antirachitic properties derived from the corresponding provitamins D. At least ten provitamins D are known, but only four vitamins D are known.

<i>Provitamin D</i>	<i>Vitamin D</i>
Ergosterol	Vitamin D ₁
Ergosterol	Vitamin D ₂
7-Dehydrocholesterol	Vitamin D ₃
22-Dihydroergosterol	Vitamin D ₄
7-Dehydrositosterol	Vitamin D ₅

Vitamin D₁ is a molecular compound of vitamin D₂ and lumisterol.

Provitamins D all belong to the sterol group with a hydroxyl in the



3-position and double bonds in ring B at positions 5 : 6 and 7 : 8. They differ from one another in the number of carbon atoms in the side-chain and the number of double bonds.

The vitamins similarly possess the same skeletal structure but different side-chains.

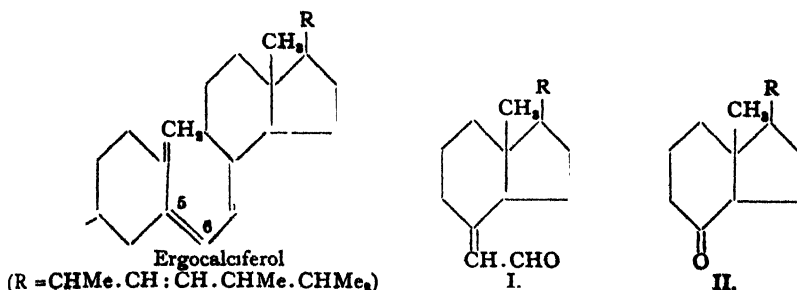
The structure of the natural vitamin known as D₃ has been deduced through researches on the synthetic antirachitic vitamin D₂, *ergocalciferol*. The known vitamins are white crystalline compounds. Vitamin D₂ melts at 115-117°, D₃ at 82-83°, and D₄ at 107-108° C. The discovery of ergocalciferol arose directly out of studies on the etiology of rickets. It was found that the disease could be cured by irradiating the patient with sunlight or ultraviolet light, and later that beneficial results were also obtained by irradiating the food consumed by the patient. Further

investigation showed that irradiation converts an otherwise inactive substance present in the food and tissues into a powerfully antirachitic compound. This inactive precursor was traced to the fats and eventually to ergosterol, largely owing to the work of Rosenheim and Webster, and of Hess and Windaus.

On ultra-violet irradiation, ergosterol undergoes a series of isomeric changes which may be summarised as follows :—



From this mixture crystalline ergocalciferol (m.p. 115-117°, $[\alpha]_D +103^\circ$ in alcohol) was isolated independently by Askew and co-workers and by Windaus. The molecular structure of ergocalciferol was deduced by



oxidative degradation and from the properties of its maleic anhydride adduct. The formula shown, which was advanced by Heilbron,¹ represents the steroid nucleus as having undergone disruption in ring B, and has a methylene group attached to C₁₀ in conjugation with the double bond at 5 : 6. Oxidation¹ of ergocalciferol with cold chromic acid gave an oily unsaturated aldehyde I; by use of permanganate the ketone II was obtained. The presence of the methylene group is supported by the production of formaldehyde on ozonisation, although it may be noted that ergosterol also yields a small quantity of formaldehyde under these conditions. Maleic anhydride forms an adduct by union with the conjugated system composed of the methylene group and the 5 : 6-double bond.

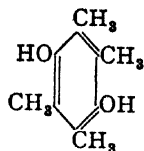
Biochemical assays showed that the ratio of rat : chick curative dose found for ergocalciferol was not the same as that for concentrates of natural vitamin D₃. The two compounds are therefore not identical as was assumed earlier. Further search for the provitamin led in 1936 to the discovery that 7-dehydrocholesterol (formula as for cholesterol, but with an additional double bond at 7 : 8) on irradiation gives an antirachitic compound² with the same biochemical assay as was found for concentrates of the natural vitamin D₃. By analogy with ergocalciferol, *cholecalciferol*,

¹ Heilbron, R. N. Jones, K. M. Samant and F. S. Spring, *J.*, 1936, 905.
Lettre and Schenck, *Ann.*, 1935, 500, 98; Windaus, Schenck and Werder, *Z. physiol. Ch.*, 1936, 242, 100.

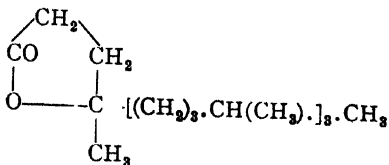
² Windaus,

The term "tocol" is now applied to the system without the alkyl substituents in the aromatic nucleus. α -Tocopherol is thus 5:7:8-trimethyltolcol, and so on.

The presence of an aromatic ring in the vitamin is shown by thermal decomposition at 350° , durohydroquinone being obtained from α -tocopherol, while the chroman structure of the second ring is supported by the results of oxidation. The most important product from α -tocopherol is a lactone to which is assigned the following γ -structure since the corresponding acid lactonises easily. The alcoholic group is tertiary since this acid when esterified does not oxidise to a keto-acid.



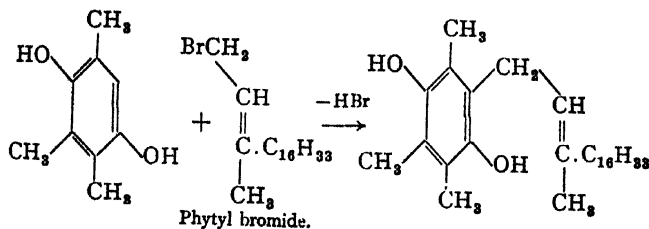
Durohydroquinone

 γ -Lactone.

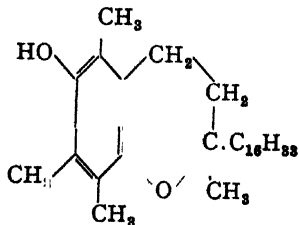
The formulæ given above have been confirmed by synthesis from phytol or its bromide and the requisite methylated hydroquinone. Normal substitution first occurs followed by ring closure which takes place when a hydrogen atom from one of the phenolic groups migrates to the ethylenic linkage.

A later synthesis¹ proved beyond doubt the presence of the chroman ring.

A fourth tocopherol, δ -tocopherol, is isolated from soya-bean oil² and is 8-methyltolcol.



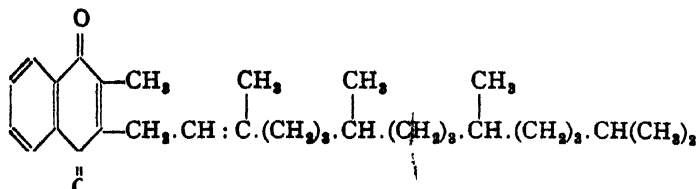
Phytol bromide.

 α -Tocopherol.

¹ For a survey by Smith see *Chem. Rev.*, 1940, 27, 297. L. I. Smith and H. C. Miller, *J.A.C.S.*, 1942, 64, 440.
² M. H. Stern, C. D. Robeson, L. Weisler, and J. G. Baxter, *J.A.C.S.*, 1947, 69, 869.

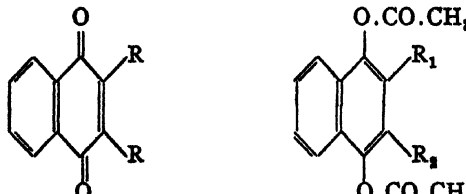
Vitamin K.¹—The term vitamin K is applied to two substances—vitamins K₁ and K₂—deficiency of which leads to prolongation of the clotting-time of blood and to hæmorrhage. The structure of the vitamin has been determined largely as the result of the researches of Doisy, Almquist and Fieser and their co-workers.

Vitamin K₁ is present in alfalfa and other green leafy tissue (cabbage, spinach, etc.) and to a lesser extent in tomato oil. It is an oil with melting-point about -20°C . It has been shown to be 2-methyl-3-phytyl-1:4-naphthaquinone.



Vitamin K

The quinone structure was indicated by various properties of the vitamin—its lemon-yellow colour, presence of two molecules of oxygen in the molecule, and the preparation of the corresponding hydroquinone

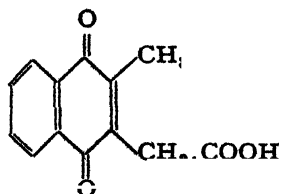


diacetate by *reductive acetylation*, a reaction characteristic of quinones. More precise information was furnished by ultra-violet absorption data since the curves of vitamins K₁ and K₂ closely resembled that of 2:3-dimethyl-1:4-naphthaquinone. These and other facts pointed strongly to an α -naphthaquinone structure and this was substantiated by the fact that of a series of quinones studied only α -naphthaquinone derivatives possessed vitamin K activity.

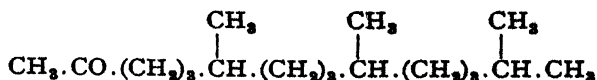
Oxidation resulted in the formation of phthalic acid and 2-methyl-1:4-naphthaquinone-3-acetic acid. The benzenoid ring is therefore unsubstituted and the vitamin must be a derivative of 2:3-dimethyl-1:4-naphthaquinone in which a hydrogen of one of the methyl groups is replaced by a long side chain, the nature of which was shown by ozonisation of dihydrovitamin K₁ diacetate when a ketone, 2:6:10-trimethyl-pentadecalone-14 was obtained. The accumulated evidence

¹ E. A. Doisy, S. B. Binkley and S. A. Thayer, *Chem. Reviews*, 1941, 28, 477.

clearly indicates the constitution of vitamin K_1 as that given above. This structure was confirmed by synthesis, the September 1939 issue of the *Journal of the American Chemical Society* containing accounts of no fewer than three different syntheses of the vitamin by several groups of workers.¹ The procedure adopted—condensation of 2-methyl- α -



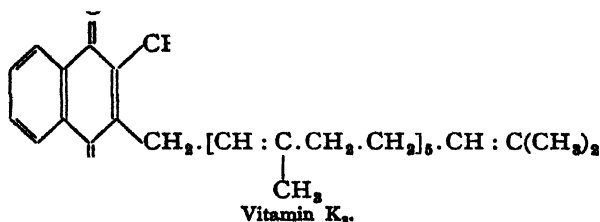
2-Methyl-1 : 4-naphthaquinone
carboxylic acid



2 : 6 : 10-trimethylpentadecalone-14.

naphthaquinone (or a derivative) and phytol (or a derivative)—may be illustrated by Almquist's synthesis from α -naphthaquinone and phytol bromide in light petroleum with zinc and acetic acid to effect the condensation.

Vitamin K_2 was isolated from putrefied fish meal and when pure is a yellow crystalline compound, m.p. 53.5 – 54.5° C. By methods similar



Vitamin K_2 .

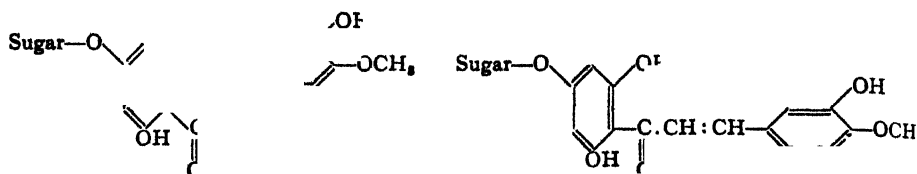
to those applied in the case of vitamin K_1 its structure has been shown to be 2-methyl-3-difarnesyl-1 : 4-naphthaquinone. It has not yet been synthesised.

It is of interest both from the academic and commercial standpoint that certain 2-methylnaphthalene derivatives are biologically active. 2-Methyl-1 : 4-naphthaquinone (vitamin K_3) is at least twice as active as vitamin K_1 . Other members of this group are 2-methyl-1 : 4-naphthalenediol diacetate (vitamin K_4) and 4-amino-2-methyl-1-naphthol hydrochloride (vitamin K_5).

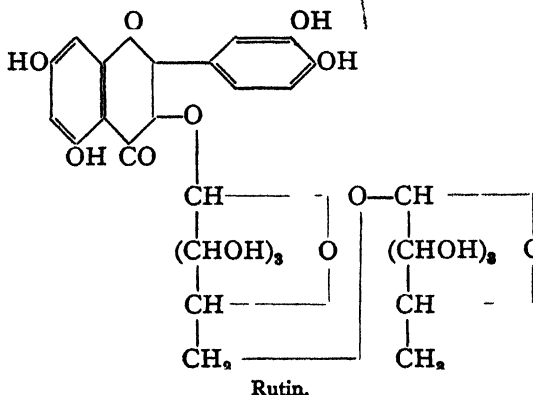
Two substances, citrin and rutin, were formerly associated with vitamin P. They have, however, no vitamin properties and the term vitamin P has been discarded. Citrin, isolated from lemons and paprika is claimed to be effective in treating diseases due to capillary fragility

¹ Almquist *et al.*, *J.A.C.S.*, 1939, 61, 2558. Binkley *et al.*, *ibid.*, p. 2558. Fieser *et al.*, *ibid.*, p. 2559.

This property was first attributed to one of its components, the glycoside **hesperidin**, 5 : 7 : 3'-trihydroxy-4'-methoxyflavanone-7-rutinoside, which probably exists in equilibrium with hesperidin chalcone.



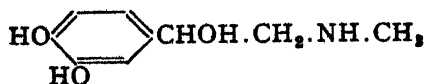
It now seems probable that the active substance is **rutin**, a flavonol glycoside, related chemically to hesperidin and obtained on the large scale from buckwheat. It occurs in yellow needles, has an indefinite melting-point and is unstable to light. Support for its formulation as quercetin-3-rutinoside comes from hydrolysis to quercetin, glucose, and rhamnose, and decomposition with alkali to phloroglucinol and protocatechuic acid.



HORMONES

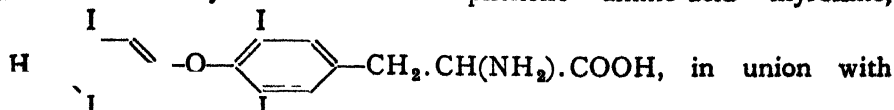
As has already been indicated, hormones are principles which are elaborated within the organism for the control or promotion of specific physiological processes. From the chemical standpoint most of our knowledge of the hormones is of comparatively recent date, although one of these compounds, adrenaline, has been known for a number of years.

Adrenaline, $C_9H_{13}O_3N$, is the hormone of the adrenal gland which brings about increase in the blood pressure. The natural product is a laevorotatory catechol derivative of the annexed formula. The physiologically less active racemic compound was synthesised in the following stages. Catechol was heated with chloroacetic acid in the presence of phosphorus oxychloride to form chloroacetocatechol, $(HO)_2C_6H_3.CO.CH_2Cl$. On treatment with methylamine this was



Commercial supplies of adrenaline may be obtained either from ox adrenals or by synthesis.

Thyroxine.—The active principle of the thyroid gland contains the laevorotatory form of the phenolic amino-acid thyroxine,

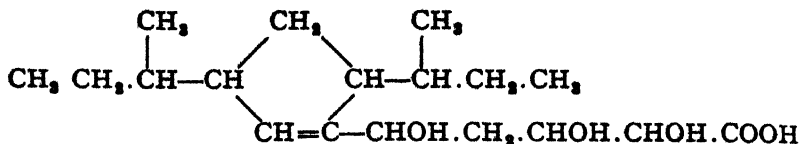


Secondary Sex Hormones.—The remarkable progress made in the study of this biologically important group has already been described in connection with the chemistry of the closely related sterols and bile acids (see p. 639).

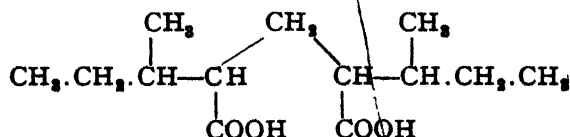
The deduction of the structure of auxin-*a* by Kögl from only 350 mg. of material is a remarkable achievement. His main points are as follows: (a) Auxin-*a* is a monobasic acid containing three hydroxyl groups. (b) With alcoholic hydrogen chloride it yields a lactone, $C_{18}H_{30}O_4$. (c) It is laevorotatory and undergoes mutarotation due to lactone formation. Equilibrium is reached in 1 to 2 hours, which suggests a δ -lactone structure as γ -lactones require much longer (see p. 315). (d) Catalytic hydrogenation adds on two atoms of hydrogen, saturating a double bond to

form an acid, $C_{18}H_{34}O_8$. (e) Treatment with alkaline permanganate ruptures the double bond and also oxidises away five carbon atoms, leaving a dibasic acid, $C_{13}H_{24}O_6$, which contains no hydroxyl groups but yields an anhydride.

From these and other facts auxin-*a* is formulated as



Auxin-*b* has $CHOH \cdot CH_2 \cdot CO \cdot CH_2 \cdot COOH$ in place of the closely related group attached to the bottom right-hand carbon of the ring in the above formula. The oxidation product mentioned under (e) is *aa'*-di-*sec*-butyl-glutaric acid, the constitution of which has been confirmed



by synthesis (Kögl, 1938). A structure such as auxin-*a* contains seven asymmetric carbon atoms and therefore can exist in no less than 128 optical isomers. Hence it is not to be expected that the compound will be easily synthesised.

ENZYMES¹

Biochemical processes are characterised by their complexity and the exact way in which each chemical change is regulated. This control is effected by organic catalysts known as **enzymes** (from the Greek "in yeast"), which are formed in plant or animal cells. They control most if not all biochemical reactions including the degradation of food constituents (carbohydrates, fats and proteins) into simpler compounds which are easily absorbed by the body, and the utilisation of these simple compounds to form tissues and produce energy.

Nomenclature.—The substance with which an enzyme reacts is called the *substrate*. For example, lactose is the substrate upon which lactase acts to form glucose and galactose.

Most enzymes have the suffix *-ase*, though with some such as pepsin and trypsin the old names still obtain. Frequently the name of an enzyme indicates the substrate upon which it acts: *e.g.* maltase acts on maltose, proteases on proteins, and amidases on carbon-nitrogen linkages (urease, arginase, purine amidases). The names of enzymes also refer sometimes to their functions: *e.g.* oxidases, deaminases, etc. Occasionally the source of the enzyme is stated: *e.g.* liver esterase.

¹ *Enzymes*, J. B. Sumner and G. F. Somers (Academic Press, New York, 1943); *Mechanisms of Biological Oxidations*, D. E. Green (Cambridge University Press, 1940).

Preparation of Enzymes.—Most enzymes are known not as definite chemical entities but in the form of active “preparations” which are obtained by the disruption of cell walls by various methods—grinding with sand or by ultra-sonic vibrations—followed by extraction with water, solutions of salts, glycerine, acetone, etc. The purification of these preparations has proved to be a laborious task; even more so is the isolation of pure enzymes especially as they are stable only within a narrow range of conditions and are extremely sensitive to change of pH and temperature. Hence the isolation of enzymes in anything approaching a state of purity involves a highly specialised technique: extraction, dialysis, adsorption, and precipitation—all at low temperatures—are employed. Highly active preparations are obtained in this way, and during the past twenty years at least twenty enzymes have been isolated in the crystalline state—*catalase*, *urease*, *trypsin*, *papain*, *ribonuclease*, *pepsin*, etc. It must be realised, however, that crystallisation, important as it is for purifying proteins and enzymes, is not necessarily a reliable criterion. For instance, crystalline swine pepsin originally believed to be homogeneous could be fractionated into at least two components, one of which on further recrystallisation was shown to be truly homogeneous. The problem of obtaining an infallible criterion of the homogeneity of protein (or enzyme) preparations is not easily solved, although much has been accomplished in recent years. The best test for homogeneity is the solubility test based on the phase rule; migration as a single component in the cataphoresis apparatus is also a good test.

Constitution of the Enzymes.—The conclusion of the earlier workers that enzymes are proteins has been confirmed in recent years by studies on highly purified specimens, often crystalline. A feature of proteins as we have seen is their high molecular weight, and it has been found that the molecular weights of enzymes are comparable.

Enzymes				Molecular Weights				Proteins			
Lysozyme	.	.	.	18,000	Lactalbumin	17,400	
Trypsin	.	.	.	34,000	Insulin	41,000	
Pepsin	.	.	.	35,500	Ovalbumin	44,000	
Pepsinogen	.	.	.	42,000	Serum albumin (horse)	70,000	
Yellow enzyme	.	.	.	73,000	Serum globulin (human)	167,000	
Catalase	.	.	.	250,000							
Urease	.	.	.	480,000							

Moreover, all crystalline enzymes give the typical protein reactions and yield on hydrolysis α -amino-acids. Hydrolysis of crystalline pepsin, for example, yields tyrosine, tryptophan, cystine, arginine, histidine, lysine, aspartic acid and glutamic acid. There can be no doubt that enzymes are proteins or at least substances closely resembling proteins.

Enzymes may be simple or conjugated proteins. The former function as enzymes without the aid of a prosthetic group and include the hydrolytic enzymes such as pepsin and trypsin. On the other hand, a number of

enzymes contain in addition to protein a prosthetic group, both being necessary for enzymatic activity. The following table gives a list of some enzymes and their prosthetic groups.

<i>Enzyme</i>	<i>Prosthetic Group</i>
Catalase	Iron-porphyrin
Polyphenol oxidase	Copper
Carbonic anhydrase	Zinc
Alcohol dehydrogenase	Coenzyme I (cozymase, diphosphopyridine-nucleotide)
Hexosemonophosphate dehydrogenase	Coenzyme II (triphosphopyridine nucleotide)
Xanthine oxidase	Flavinadenine nucleotide

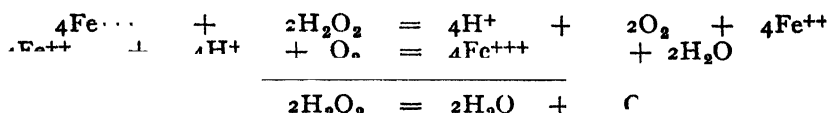
In some cases it will be noted that the prosthetic group is a complex organic molecule bound loosely or firmly to the protein carrier. When such prosthetic groups are obtained in the free state as low molecular weight diffusible substances, usually of known constitution, they are known as co-enzymes.

Properties of Enzymes—Enzymatic Action.—Enzymes are distinguished by their catalytic activity and not by orthodox chemical tests and reactions. They are unstable under most conditions and are very dependent on factors such as temperature, acidity, etc. For each enzyme there is a particular *pH* value at which its catalytic activity is at a maximum. This is known as the *optimum pH*. Similarly the temperature at which its maximum activity occurs is the *optimum temperature*. For most animal enzymes this lies in the neighbourhood of 37°. Lowering of temperature results in decreased activity and at 0° C. most enzymes are almost inactive. At 100° C. most enzymes are destroyed, only a few of low molecular weight such as ribonuclease or lecithinase A being stable in a boiling solution.

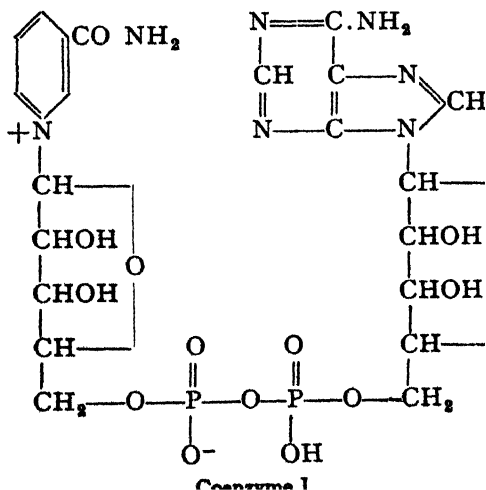
Enzymes differ from other catalysts by their specificity. Some attack only one substance; *urease*, for instance, attacks only urea. Others are specific for a series of compounds containing certain groupings, e.g. *deaminases*, *decarboxylases*, *esterases*, etc. Enzymes of the second type, however, do not attack all compounds of a certain class; not only *structural* but also *configurational* considerations must be taken into account. For instance, the α -glucosidase, *maltase*, will not attack the β -glucoside, cellobiose. The simplest way to account for this specificity is to assume that the structures and configurations of the enzyme and substrate are such that close contact can be effected between the two. Indeed it may well be that the first step in enzyme catalysis is compound formation between enzyme and substrate, and there is considerable evidence to support this assumption. For example, *invertase* is much less sensitive to heat when in presence of its substrate sucrose the enzyme being protected to a certain extent by its combination with the sugar. It is highly probable that this combination between enzyme and substrate is due to the presence of functional groups such as the amino and carboxyl

Fumarase, which controls the reaction, $(-)\text{-malate ion} \rightleftharpoons \text{fumarate ion} + \text{H}_2\text{O}$, is readily deactivated by small quantities of certain dyes, but is completely protected from dye poisoning by its substrates (fumarate and $(-)\text{-malate ions}$). Since it is known that these substrates do not combine with the dyestuffs, it follows that their protecting effect is due to combination with the enzyme itself; the functional groups of the enzyme by participating in the formation of enzyme-substrate compounds are prevented from reacting with the dyes.

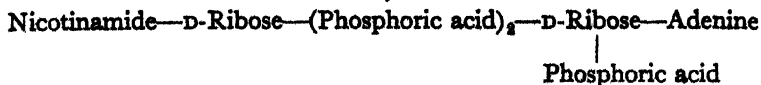
As has already been stated many enzymes contain not only a protein but also a prosthetic group or coenzyme. In such cases enzymatic activity is associated with the combination of a specific protein with a specific prosthetic group. The function of these prosthetic groups is known in some cases with a fair degree of certainty, and is exemplified by *catalase*, which controls the decomposition of hydrogen peroxide into oxygen and water. The prosthetic group in this case is hæmatin, the organic iron complex found in hæmoglobin. According to Keilin and Hartree, the iron of catalase is in the ferric state and in presence of hydrogen peroxide is reduced to the ferrous state while oxygen is liberated. The ferrous complex is then oxidised by oxygen to its original state and the cycle



The coenzymes are stable, dialysable organic compounds whose structures in many cases are known. The first coenzyme to be isolated was *cozymase* (*coenzyme 1*, *diphosphopyridine nucleotide*), the thermostable organic component of *zymase*. Its structure is:—



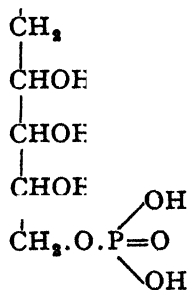
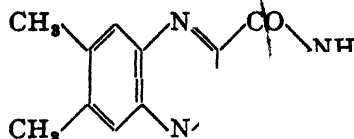
Another coenzyme with a very similar structure is *coenzyme II* (*triphosphopyridine nucleotide*), which, however, contains three phosphoric acid residues.



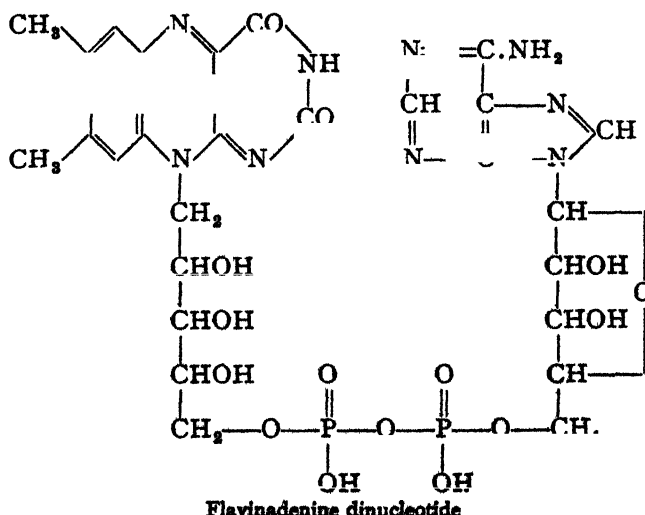
Coenzyme II.

In the *flavoproteins* (*yellow enzymes*) the prosthetic group is either riboflavin phosphate (lactoflavin phosphate) or flavinadenine dinucleotide (alloxazine adenine dinucleotide). Both these compounds contain the iso-alloxazine nucleus.

This dinucleotide is very similar in chemical constitution to coenzyme I, the main difference being the presence of the isoalloxazine nucleus instead of nicotinamide.

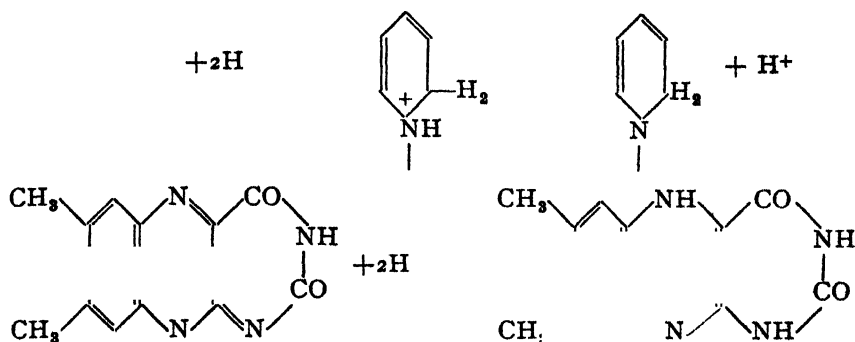


Riboflavin phosphate

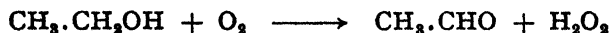


The first crude yellow enzyme was isolated in 1932 by Warburg and Christian and two years later Theorell succeeded in obtaining it in the crystalline form. The enzyme can be split into two components, a protein and a coenzyme in the form of a yellow dye which was shown to be riboflavin-5-phosphoric acid. Neither the protein nor the coenzyme possess enzymatic activity, but R. Kuhn showed that the monophosphoric ester of synthetic riboflavin on combination with a specific protein of the yellow enzyme yielded the active yellow enzyme.

Some coenzymes function in enzymatic reactions as hydrogen acceptors; hydrogen is removed from the substrate and the coenzyme is reduced to the dihydro form. The groupings responsible for this oxidation are the heterocyclic pyridine and isoalloxazine nuclei.



As an example, the oxidation of alcohol to acetaldehyde by means of the enzyme *alcohol dehydrogenase* and its coenzyme (coenzyme I) may be outlined.



The first stage is probably the formation of a loose complex between alcohol and the enzyme in which the two atoms of hydrogen are transferred from the alcohol to the coenzyme. The initial products are acetaldehyde and dihydrocoenzyme I. The reduced coenzyme can then be oxidised back to the coenzyme by one of the flavoproteins, two hydrogen atoms being transferred to the isoalloxazine ring. The reduced flavoprotein may then be oxidised spontaneously by molecular oxygen, hydrogen peroxide being formed, or it may be oxidised more rapidly by the pigment *cytochrome* which is found in many animal cells. The oxidation-reduction cycle then begins again.

One other feature of enzymatic action must be mentioned—its *reversibility*. In other words, enzymes are able not only to break up a substance into its components but also to effect the reverse synthetic process. A hydrolytic enzyme, for example, is able both to split its substrate into hydrolysis products by the addition of water and also to synthesise the original compound by the removal of water from these products. Many enzymatic reactions proceed so far in one direction that

there is little or no evidence of the reverse reaction. A very good example of the reversibility of enzyme catalysed reactions is to be found in the case of the enzyme *phosphorylase* which catalyses the reaction



According to the conditions used the enzyme may be employed for the preparation either of polysaccharide or of glucose-1-phosphate.

Some Typical Enzymatic Reactions

Hydrolysis

Lipase	Fats → Fatty acids and glycerol
Pepsin	Proteins → Proteoses and peptones
Trypsin	Proteins → Polypeptides and amino-acids
Amylase	Starch → Maltose
Lactase	Lactose → Glucose and galactose

Oxidation-Reduction

Catalase	Hydrogen peroxide → Water and oxygen
Tyrosinase	Tyrosine → Melanin
Xanthine oxidase	Hypoxanthine → xanthine → uric acid

Evolution of Carbon Dioxide

Carboxylase	α-Keto acid → Aldehyde and carbon dioxide
Carbonic anhydrase	Carbonic acid → Carbon dioxide and water

Other Reactions

Phosphatases	Transfer or removal of phosphate groups
Emulsin	Amygdalin → Glucose, benzaldehyde, and hydrocyanic acid

XII

Chemotherapy ¹

Until the end of the last century chemicals from vegetable or animal sources or the same chemicals prepared synthetically were the mainstay of curative medicine. A change, however, was foreshadowed by the discovery of Ehrlich and Guttman in 1891 that methylene blue possesses anti-malarial action, and great possibilities were envisaged when in 1899 it was found that the synthetic compound *aspirin*, acetylsalicylic acid, relieved pain and at the same time did not possess the toxicity of drugs such as salicylic acid or the depressing effect of sodium salicylate. The discovery of aspirin may well be said to have ushered in a new era in medical science; synthetic drugs of great efficiency for various diseases are now commercial products and an astounding number of organic chemicals has been synthesised for the sole purpose of discovering whether or not they possess remedial properties.

¹ *The Basis of Chemotherapy*, by T. S. and E. Work (Oliver and Boyd, Ltd., 1948). W A Sexton, *Chemical Constitution and Biological Activity* (Spon, Ltd.).

Chemotherapy, or the treatment of parasitic diseases by means of chemical drugs, has made great progress during the last few years. Such diseases may be caused by the presence in our bodies of large parasites, *e.g.* tape-worms, liver flukes and hook-worms, or of parasites of microscopic dimensions. Among the latter are included (a) **protozoa**, animal micro-organisms with relatively large and highly developed cell structures, (b) **bacteria** and *fungi*, which are appreciably smaller than protozoa and are generally classed as vegetable micro-organisms, and (c) the exceedingly small **filter-passing viruses**, which are so minute as to pass through the pores of unglazed porcelain.

Parasitic Diseases

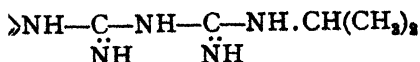
<i>Protozoa</i>	<i>Bacteria</i>	<i>Viruses</i>
Malaria	Septicæmia	Common cold
Sleeping sickness	Puerperal fever	Measles
Relapsing fever	Pneumonia	Mumps
Syphilis	Meningitis	Smallpox

In the treatment of any disease a remedy is sought which will kill the parasites without unduly endangering the life of the patient, and although notable successes had already been achieved in this field they have been limited until recently to diseases originating in the presence of large parasites and of protozoa.

Protozoal Diseases.—Some examples of protozoal diseases, together with their remedies, are tabulated below.

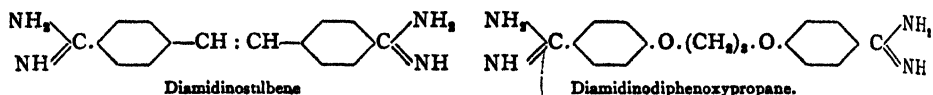
Malaria . . .	Quinine, paludrine
Syphilis . . .	Salvarsan (neoarsphenamine), sulpharsphenamine
Sleeping sickness .	Atoxyl, tryparsamide, germanin (see p. 874)
Yaws	Neoarsphenamine
Kala-azar . . .	Tartar emetic, amidines
Amœbic dysentery	Emetine

Malaria is probably the most wide-spread of all diseases, since it is estimated that about one-third of the world's population suffer from it at one time or another during their lives. For two centuries the chief remedy has been quinine, but many attempts have been made to obtain effective synthetic substitutes. Two synthetics discovered by the Germans, *plasmoquin* (*pamaquin*), a quinoline derivative, and particularly *mepacrine* (*atebrin*), an acridine derivative, were extensively used. Intensive research in many laboratories led to the synthesis of many substituted quinolines and acridines in the hope of obtaining still more effective anti-malarials. Success, however, was limited until Curd and Rose of Imperial Chemicals (Pharmaceuticals), Ltd., prepared an anti-malarial of a novel type to which they gave the name **paludrine**, since malaria is most common near marshes (*Latin*, palus, paludis). It has the following formula :



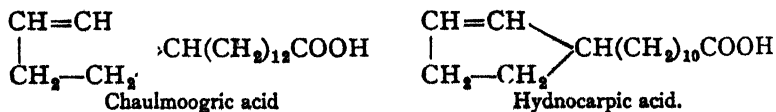
Unlike quinine and mepacrine, paludrine is a true prophylactic. It is more effective against malaria than quinine and possibly mepacrine. Unlike the latter it does not cause nausea nor does it stain the skin yellow, and as it is said to be easy to manufacture it should be cheaper than the other drugs.

Another outstanding advance was the discovery by Yorke and his collaborators that certain **amidines** possess trypanocidal action. Investigation has shown that the most effective are 4 : 4'-diamidinostilbene, 4 : 4'-diamidino- α - γ -diphenoxypropane, and 4 : 4'-diamidino- α : ϵ -diphenoxypentane. Diseases such as sleeping sickness and kala-azar have been successfully treated with these compounds.



The important impact which these so-called tropical diseases have on world affairs may be gauged by considering one of the most widespread, malaria. Various estimates have been given, but it is safe to say that between 2 and 3 million deaths, half of them in India, result annually from this disease. In the Second World War about 80 per cent. of the Allied troops in the East at one period succumbed to malaria and the casualties from malaria in the Sicilian campaign were greater than those caused directly by the fighting.

Bacterial Diseases.—In most of the above cases of protozoal disease the remedies are highly effective and their discovery represents an invaluable contribution to medicine. Until a few years ago, however, little corresponding progress had been made in the chemotherapeutic treatment of bacterial diseases, which are an even greater scourge to mankind than those of protozoal origin. Leprosy, a bacterial disease due to *B. lepra*, was formerly treated by oral administration of the nauseating *chaulmoogra oil*. Real progress with this disease has only been made since 1910, when the method of injecting *sodium hydnocarpate*

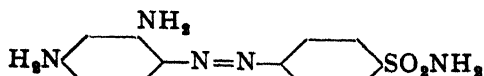


into the muscles was introduced, this salt being later replaced by the more effective **ethyl chaulmoograte**. In this way cures can now be effected in 40 to 50 per cent. of the cases.

Sulphonamides

In 1935 Domagk, working in collaboration with the organic chemists Mietzsch and Klarer and the Bayer Company at Elberfeld, Germany, aroused widespread interest in the medical world by making known the astonishing results obtained with **prontosil** in curing certain

streptococcal infections. While investigating the use of azo dyes in this connection Domagk discovered that azo compounds containing sulphonamido groups had a marked beneficial effect. **Prontosil**, the hydrochloride of 4-sulphonamido-2':4'-diamino-azobenzene (see annexed formula) proved to be the most active of the very large number of sulphonamido dyes under examination.



In their various strains streptococcae are responsible for the majority of septic conditions such as are present in blood-poisoning, wound infections, and many major diseases, including erysipelas, scarlet fever, puerperal fever, pneumonia, cerebrospinal meningitis, gonorrhoea, and tonsillitis. In most cases the infection is due to *Streptococcus pyogenes*, the β -haemolytic streptococcus. Pneumonia is more generally caused by the *pneumococcus* or *Streptococcus pneumoniae*. It will be readily understood that the discovery of drugs capable of being used with success in the treatment of any of these bacterial diseases represents an advance in chemotherapy of the greatest significance.

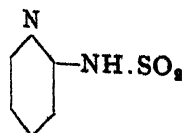
Later developments furnish an interesting example of the manner in which such problems are attacked by research chemists working in collaboration with pathologists. It was found in France that prontosil breaks down in the human body to form *p*-aminobenzene-sulphonamide, and that the latter compound was an equally active chemotherapeutic agent. The importance of this lies in the fact that *p*-aminobenzene-sulphonamide, now usually called **sulphanilamide**, has long been known to chemists and is not a patented product.

It is, moreover, cheap and can therefore be used in place of the highly priced prontosil.



After it had been shown that benzene sulphonamide itself, with no amino group in the para position, was completely inactive, research was directed towards the investigation of derivatives of sulphanilamide in which hydrogen of the amino groups was replaced by substituents. Among numerous compounds of this type two of outstanding activity have been found, namely **sulphapyridine** (M & B 693), and **sulphathiazole**, both prepared in the laboratories of May and Baker.

A homologue of the latter, **sulphamethyl-thiazole** (M & B 760a) is also used, containing a methyl group in place of the hydrogen atom marked with an asterisk.



Sulphapyridine (M & B 693)

-NH₂

HC

NC-NH·SO₂

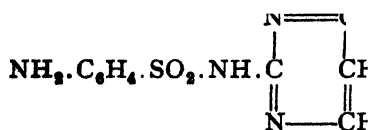
-NH₂

*HC

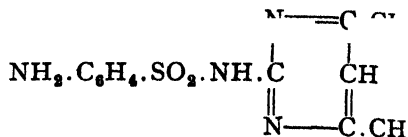
N

Sulphathiazole.

Medical evidence up to the present time indicates that in the treatment of most streptococcal diseases sulphanilamide, prontosil and sulphapyridine are equally and remarkably effective. Sulphanilamide is frequently used because of its cheapness, but, in cases of pneumonia, sulphapyridine, etc., are used. Sulphathiazoles are expensive to manufacture, but have the advantage that they produce less nausea. Other important members of the series which have been much used are sulphapyrimidine and sulpha-4 : 6-dimethylpyrimidine.

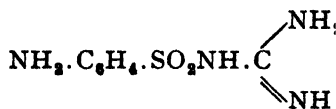


Sulphapyrimidine

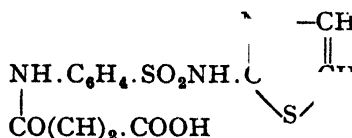


Sulpha-4 : 6-dimethylpyrimidine.

Sulphaguanidine has proved of great value in cases of dysentery on account of its poor absorption into the blood stream. Another sulphonamide which has been used for this purpose is succinylsulphathiazole.

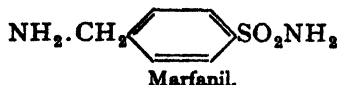


Sulphaguanidine



Succinylsulphathiazole

All the above drugs contain the grouping $-\text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \text{NH}-$, and it would appear that this is the essential structure for this type of drug. An exception, however, is to be found in *marfanil*, which is of value in cases of gas gangrene. It is remarkable for its stability and extremely low toxicity; it is unique in its action against anaerobic bacteria; and unlike the other sulphonamides its action is not inhibited by pus. Unlike the other sulpha compounds it is not a derivative of aniline but of benzylamine.



Sulphanilamides are administered in comparatively large doses by mouth or by dusting on an infected wound, and the results are usually rapid and decisive. Astonishing reductions in mortality have been recorded by their use in puerperal fever, pneumonia and cases of severe blood poisoning. The mortality rate for cerebrospinal meningitis or spotted fever, which was about 60-70 per cent., has latterly been lowered to the order of 30 to 40 per cent. by use of serums. Sulphanilamide, however, has now brought this rate down to the neighbourhood of 2 per cent. Sulphapyridine, which is reducing the death rate in pneumonia cases to about one-third of the earlier figure, has also proved to be of special value as a remedy for gonorrhœa, a disease for which no satisfactory treatment

had hitherto been evolved. Encouraging results have already been obtained with infections due to *B. coli* and with plague. Among other bacterial diseases which have not yet been successfully treated by chemotherapeutic methods are tuberculosis, whooping cough, typhoid, paratyphoid and cholera.

One of the great disadvantages of serums is that they are very specific in their reaction. Not only must different diseases, if they are amenable to this type of treatment, be countered by use of their particular serums, but a given disease may be caused by different strains of the same bacillus, in which case it is generally necessary for the latter to be identified before an appropriate serum can be selected. There are, for example, no less than 34 known strains of *pneumococcus* which may give rise to pneumonia. Fortunately it has been found that sulphapyridine is equally effective against all of these. Further research indicates that the strains differ from one another only in the nature of the outer protective coverings which enclose the pneumococcus protoplasm. The outer layers are composed of material resembling the vegetable gums and can apparently be permeated by sulphapyridine by virtue of the pyridyl group which differentiates it from unsubstituted sulphanilamide.

Antibiotics : Penicillin

Antibiotic is the term introduced by S. A. Waksman to denote a chemical substance which is formed during the growth of a micro-organism such as a fungus or bacterium and kills or prevents the growth of other micro-organisms. It has long been known that certain fungi and bacteria can prevent the growth of other micro-organisms and in 1870 this was clearly recognised by William Roberts. That this property is due to the formation of chemical substances was shown in 1885 by the Roumanian Babès.

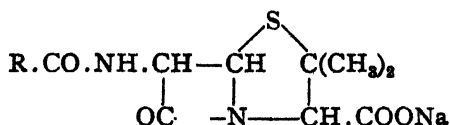
The first antibiotic to find extensive use was Gramicidin which was isolated in 1941 by Dubos and Hotchkiss.

The full therapeutic possibilities of antibiotics, however, were not translated into practice until, following its discovery by Fleming and its subsequent investigation by Florey, **penicillin** was produced on the industrial scale. It inhibits the growth of streptococci at a dilution of 1 in 30,000,000 and is non-toxic—a unique combination of therapeutic potency and innocuity. It is extremely active against streptococci, staphylococci, pneumococci, meningococci and gonococci, but it is inactive against tubercle bacilli. It has the advantage over the sulphonamides that its action is not inhibited by pus.

Penicillin, produced from *Penicillium notatum*, is acidic and may be isolated as the barium or strontium salt. It is soluble in water and is optically active. Its aqueous solutions are stable only between pH 5.5 and 7.5. Penicillin itself is very sensitive to heat, oxidation, many chemical reagents and some enzymes. Its therapeutic importance was heightened

by the Second World War and led to intensive chemical investigations both in America and this country.

Early in 1946 the formulæ of the penicillins was published.



Several penicillins are known. All have the above generic formula and differ only in the nature of R.

Penicillin I. R = CH₂.CH : CH.CH₂.CH₃

Dihydropenicillin I. . . R = *n*-amyl

Penicillin II. R = -CH₂.C₆H₅

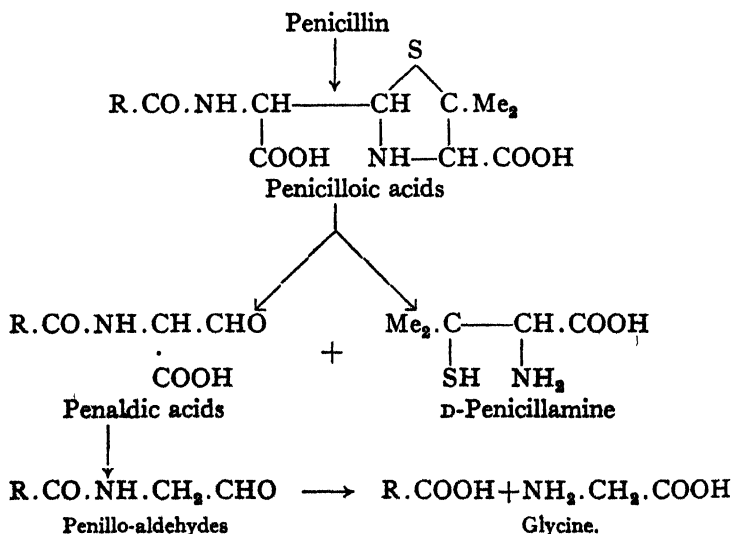
Penicillin III. R = -CH₂.C₆H₄.OH(*p*).

Penicillin IV. R = *n*-heptyl

Penicillin is an unstable tautomeric substance. The most notable feature of its constitution is the four-membered lactam ring which has not so far been found in any other natural product. This ring is readily opened, and this is the cause of the instability of penicillin.

The constitution of penicillin has been derived from a number of chemical reactions of which the following are important.

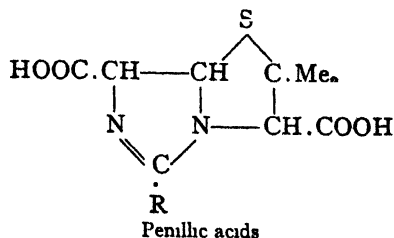
With alkali or a specific enzyme, *penicillinase*, the lactam ring undergoes hydrolytic fission to give *penicilloic acids*. The thiazolidine ring in these acids in contrast to that in the penicillins undergoes ring-fission readily with aqueous mercuric chloride (a standard reagent for the



thiazolidine nucleus) with the formation of *penicillamine* and *penaldic acids*. It will be noted that penicillamine has the "unnatural" (D) configuration. It is a β : β-dimethylcysteine and its structure has been

shown by various methods including synthesis. The penaldic acids easily lose carbon dioxide (decarboxylation) and yield *penillo-aldehydes* the structure of which follow from oxidation and then hydrolysis to carboxylic acids and glycine.

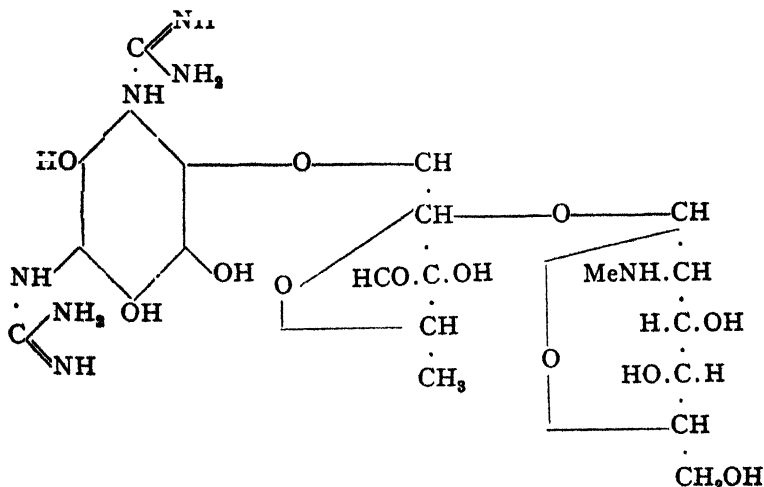
These chemical reactions supplemented by physical evidence such as crystallographic studies supply the main evidence for the above constitution of the penicillins.



In acid solution penicillin loses its biological activity by undergoing a molecular rearrangement to *penillic acids*.

Penicillin I was synthesised independently in Oxford University and the Merck Institute in New Jersey in 1945, and two years later penicillin II was synthesised by a team at Cornell University. These syntheses, however, are of small value since the yields amount to only 0.1 per cent.

Streptomycin was discovered by Waksman and his co-workers in their studies of salt organisms. Its importance lies in its high activity against *Mycobacterium tuberculosis* and in particular its effectiveness in the treatment of meningeal tuberculosis. Its structure was elucidated chiefly by the Merck workers and is of interest in that it is a diguanidino derivative united through a glycosidic linkage to a disaccharide composed of N-methyl-L-glucosamine and another sugar *streptose*.

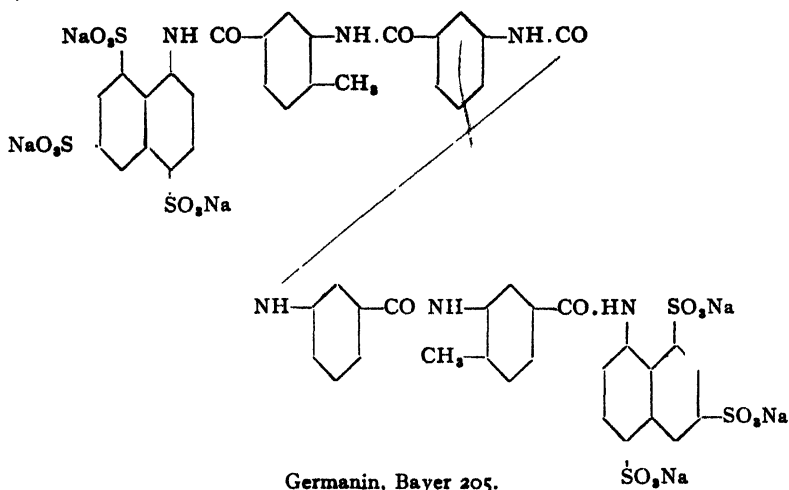


Streptomycin

A number of other mould-metabolism products possessing anti-bacterial properties are known. Among these may be mentioned citrinin, fumigatin, puberulic acid, penicillic acid (not related to penicillin), patulin, gramicidin, notatin, etc. Most of these possess toxic properties.

Virus Diseases in general have not yet been attacked with any great success by chemotherapeutic methods.

Unfortunately, no working theory has yet been developed to explain why one particular arrangement of atoms should be more effective than another in attacking a given micro-organism. Why, for example, is the *p*-aminobenzene-sulphonamide group so amazingly active against streptococcal infections? Why is the efficiency of germanin (formulated below) in the treatment of sleeping sickness wholly dependent on two



otherwise insignificant methyl substituents, in the absence of which the remaining molecular structure is practically inactive? Until some reply to questions such as these is forthcoming, chemotherapy can only advance slowly and along empirical lines.

XIII

Plastics or Synthetic Polymers¹

The remarkable success of the phenolic aldehyde resins introduced by Baekeland resulted in an enormous development in the group of compounds known as plastics or synthetic resins. Under this heading are included not only materials which become plastic on heating, but also hard infusible products which at some stage in their preparation have plastic properties by means of which they can be moulded into

¹ P. D. Ritchie, *Chemistry of Plastics and High Polymers* (Cleaver-Hume Press, Ltd., 1949).

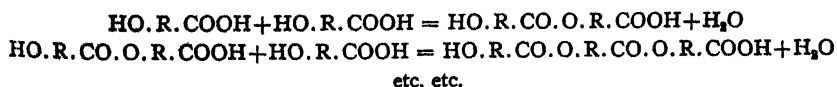
finished articles. They are produced by the polymerisation or condensation of relatively simple compounds and represent a number of different chemical types. High polymers are unique among organic materials in possessing an exceptional degree of tensile strength, elasticity, hardness and toughness, as has long been recognised in the case of the natural polymers, silk, cotton, rubber and shellac. By the use of synthetic methods it is now possible to prepare on the large scale products with any of these valuable mechanical qualities.

Plastics vary greatly in their physical properties, ranging from black or bright in colour to glass-clear and from a viscous or rubbery consistency to hard or even brittle. All are capable of being employed for the manufacture of moulded articles, although some are better adapted for use as protective finishes in lacquers and dopes, or for bonding loose materials such as asbestos and mica in a form which will withstand high temperatures (*e.g.* for insulations, brake linings). Owing to their excellent electrical properties many members of the group are used as insulating materials; others such as *perspex*, which are transparent and colourless, may be moulded directly into optical lenses or used as windows in aircraft. The solid forms may be not only moulded but also sawn, cut, turned and polished.

Polymerisation and Polycondensation

The chemical properties of organic substances are to a great extent dependent not on the carbon chains or rings but on the *functional groups* in the molecule—COOH, OH, NH₂, etc. Each of these groups has its own characteristic reactivity, and reactions such as esterification are simply the interaction of the functional groups of different molecules. Most of the reactions we have encountered in this book involve interaction between functional groups to give products in which the reactivity of these groups has been neutralised. Acetic acid and ethanol, for example, give ethyl acetate which has neither the properties of an acid nor of an alcohol. In other words the product is incapable of combining with either reactant.

Quite another state of affairs obtains when two molecules each with two functional groups react. An example of this kind is found in the bifunctional hydroxy acids, HO.R.COOH, containing the two active groups hydroxyl and carboxyl. Two such bifunctional compounds or *monomers* interact to give a product which is also bifunctional and can undergo further esterification.



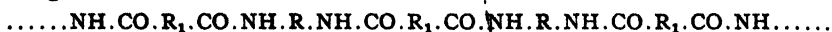
In this way *polyesterification* occurs and provided ring formation is avoided a *macromolecule* results in the form of a long chain polymer of the structure:



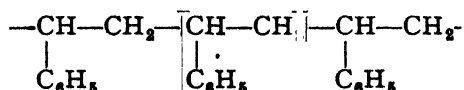
A similar chain reaction occurs when a glycol and a dibasic acid (both bifunctional) are heated together,



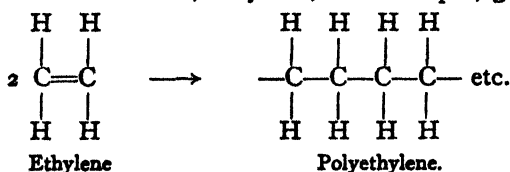
A detailed investigation of such types was made by Carothers and his co-workers, which led to the examination of polyamide chains containing hydrocarbon radicals linked by $\text{CO} \cdot \text{NH}$ -groups. Carothers found that the plastic properties of the polyamides are closely related to the lengths of the hydrocarbon radicals, and the work culminated in the development of the synthetic silk *Nylon* and the fibre *Extol*. *Nylon* can be obtained finer, stronger and more resistant than natural silk, which it resembles in molecular structure. As at present manufactured (see p. 881) it is a condensation product of hexamethylene diamine with adipic acid, and is of the general structure



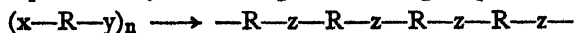
Olefins also act as bifunctional compounds. An important example of this is styrene, $\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH}_2$, the polymerisation of which is believed to proceed by way of the activated form $-\text{CH}(\text{C}_6\text{H}_5) \cdot \text{CH}_2-$ to yield chains of the type



The terms polymer and polymerisation have undergone considerable change from their original meaning. In the older sense a substance underwent polymerisation when it yielded a product or polymer of the same empirical formula but different molecular weight. Many polymers still conform to this definition, ethylene, for example, giving polythene:



Polythene is obviously an integral multiple of a single repeating unit. W. H. Carothers termed this **addition polymerisation**. On the other hand the polyesterification mentioned earlier gives rise to a macromolecule by a series of condensations. This is essentially the interaction of a number of bifunctional molecules of the type $x-\text{R}-y$ in which the functional groups x and y react to give a new group z .



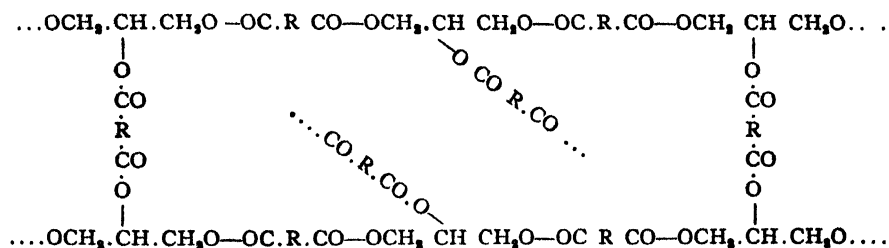
Carothers termed this process of chain building **condensation polymerisation**. In both types of product the macromolecule is composed entirely or almost entirely of repeating units.



It should be noticed that macromolecules may be composed of two or more different repeating units and are then known as **copolymers**. We have already encountered an example of copolymerisation in Buna-S (p. 424) in which butadiene and styrene units alternate along the chain.

All the above cases refer to monomers having only two active functions, and the resulting polymers are mixtures of long chain molecules of various lengths. The structural pattern may thus be described as one-dimensional. Such polymers are in general both soluble in organic solvents and fusible; all products of this nature are **thermoplastic**.

So far we have considered the polymerisation of molecules to form long chains. It is, however, possible to introduce another factor, namely, *cross-linking*, which modifies profoundly the properties of the products. This is accomplished by reacting molecules with higher functions than two, as in the combination of glycerol (trifunctional) and a dibasic acid. Instead of the simple linear polyester obtained with glycol, the glyceryl ester is a rigid three-dimensional structure in which the long main chains are interconnected by cross-links in all directions, as symbolised in the following diagram where the inclined chains may be supposed to bind parts of the molecule situated behind or in front of the main diagram. This kind of product is insoluble and infusible and belongs to the group of **thermosetting resins**. It cannot be remoulded by the further application of heat and pressure, and solvents are no longer able to effect a separation of the chains, although a certain amount of swelling may occur in some cases. Complete elimination of swelling can



be achieved by increasing the number of cross-links, but this also tends to make the product more brittle.

In some polymerisations and condensations the linear reaction predominates under mild experimental conditions, even when one of the reacting molecules has more than two active functions. This is useful technically as it allows the reaction to be carried out in two stages. Products varying by degrees from the readily soluble and fusible to the insoluble and infusible can thus be prepared according to the extent of interaction (see phenol-aldehyde condensations). Staudinger has demonstrated the remarkable effect of polymerising styrene to which even so small a proportion as 0.01 per cent. of *p*-divinylbenzene, $\text{CH}_2 : \text{CH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{CH}_2$, has been added. The molecules of the

latter, being polyfunctional, provide cross-links between the linear polystyrene chains, with the result that whilst the product outwardly resembles polystyrene it differs from it in being insoluble in solvents, although undergoing swelling in their presence. Pure divinylbenzene on polymerisation yields a hard brittle product, which does not swell in solvents and is readily powdered.

Manufacture of Plastics

In the industrial processes the monomeric starting material, as has already been stated, is not necessarily a homogeneous substance but may be a mixture of two or more compounds. Polymerisation is effected by heat or light and is often assisted by the addition of *accelerators* (acids, bases, benzoyl or acetyl peroxide, diisobutylene ozonide). Use is also made of *retarders* (picric acid, sulphur, nitro and nitroso compounds) which increase the time required for complete polymerisation, and of *inhibitors* (hydroquinone, phenyl naphthylamines) which cause a preliminary period of inhibition during which no polymerisation occurs. The various monomers undergo polymerisation at widely differing rates, and the change may be completed in a few seconds or may require hours. In many cases it is desirable to effect partial polymerisation before submitting the product to final treatment in the mould or other process. For these reasons it is essential to have the reaction under efficient control.

When a resin of this type is treated with a solvent, the molecules of the latter are also attracted to those of the polymer by the van der Waals forces. As a result the solvent penetrates slowly into the mass, which at first swells and then as the chains become separated eventually passes into solution. Small amounts of a selected solvent are often added to a polymer for the purpose of softening the material or to render it less brittle. For this reason camphor is added to pyroxylin in the manufacture of celluloid. But such **plasticizers** are generally non-volatile liquids, *e.g.* triphenyl and tricresyl phosphates, butyl phthalate and triacetin (glyceryl triacetate).

Thermoplastic Resins

The plastics of this type are soluble in organic solvents; they may be shaped and reshaped repeatedly by the application of heat followed by treatment of the softened or liquid mass in a mould. In this class are included most of the earlier known natural plastic and wax compositions, such as *shellac* (still used for gramophone records), *bitumen plastics* (screw stoppers of bottles, etc.) and *cellulose plastics* (celluloid, cellulose acetate and ethers) as well as the more recent glass-like plastics prepared from the vinyl derivatives styrene, *acrylic* and *methacrylic esters*.

The thermoplastic resins often differ from cellulose in giving no definite X-ray diffraction pattern, and it must be assumed that in these cases the long chain molecules are not orientated in parallel lines but

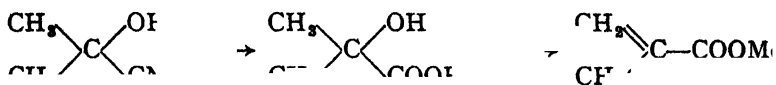
have a tangled arrangement. The van der Waals forces of attraction between macromolecules of this kind are very considerable, however, so that after being softened by heat the cooled viscous mass may be stretched out into long threads, in which owing to partial slipping of the chains past each other the molecules become to some extent oriented in parallel directions.¹ This orientation leads to an increase in lustre and tensile strength (see Nylon, p. 881).

Celluloid, one of the earliest representatives of this group, has already been described (see p. 343).

Cellulose acetate is prepared for use by being mixed with the necessary amount of solvent and a plasticizer. It then forms a doughy mass from which excess of solvent is removed by working between hot rollers. Thick irregular sheets termed "hides" are thus obtained. For moulding purposes these are cut into fine chips and mixed with the required fillers and colouring matter. The thin sheets employed for wrappers are made by evaporating a dilute solution on a flat metal surface from which the film is subsequently stripped (*continuous film casting process*). The solvent is recovered for further use.

The newer *glass-like plastics* are vinyl derivatives which are most conveniently described under the individual monomeric starting materials.

Methyl methacrylate is employed in the production of *diakon* moulding powder and of *perspex*. For this purpose acetone cyanhydrin is converted into methacrylic ester by treatment with sulphuric acid at 100° to 110° followed by reaction with methyl alcohol.



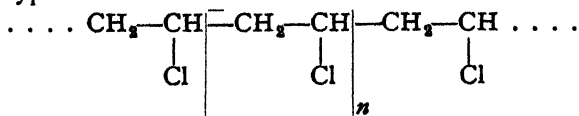
Polymerisation of the monomer may be effected in different ways, two of which are used industrially.

1. Granular polymerisation process which gives a product consisting of tiny spheres. This is used for mouldings and dentures.
2. Polymerisation-casting process. The monomer with a trace of catalyst is polymerised at a moderate temperature between glass plates. Sheets of *perspex* are produced in this way.

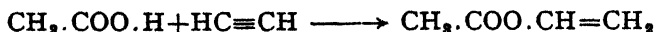
The chief characteristics of *perspex* are its remarkable clarity, low specific gravity (1.19) and excellent mechanical and electrical properties. It is used for making electric fittings, telephones, dentures, etc., and protective windows for aircraft. Lenses of any desired prescription are readily moulded in a finished form; they are rather more easily scratched than glass but may be surface-hardened by means of a clear uniform layer of silica deposited in a high vacuum, care being taken to screen the lens from direct heat. The polymer is also used for lacquers and dopes.

¹ J. R. Katz, *Trans. Farad. Soc.*, 1936, **32**, 77. Compare also stretched rubber, p. 426.

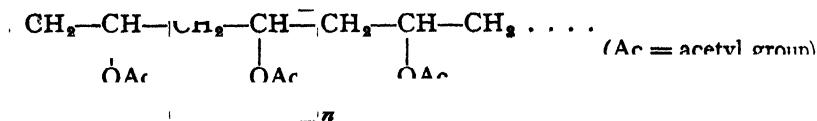
Vinyl chloride polymers are denser (sp. gr. 1.4) than perspex but are non-inflammable and more resistant. Owing to its higher melting point the product must be treated with a plasticizer before being used in moulding. Polyvinyl chloride is employed for the manufacture of chemical plant, pipe lines, water-resisting sheets and flexible insulation for wires and cables. The molecules are represented as containing chains of the type



Vinyl acetate can be prepared in 80 per cent. yield by the direct combination of acetylene and acetic acid in the presence of a mercury salt catalyst.



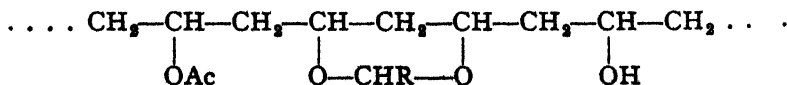
It polymerises on heating to form a clear transparent mass, sp. gr. 1.2 and the process may be so controlled as to give products (*Gelvas*) of widely differing viscosities. The average molecular weight may range from about 5000 to 100,000. Polymerisation is represented as leading to chains of the following structure :



Polyvinyl acetate is somewhat low in melting point for use in moulding, but is employed for lacquers, finishing compositions and adhesives.

Vinyl acetate and vinyl chloride are also used in admixture for the preparation of polymers (*mixed or co-polymers*). By varying the proportions of the ingredients it is possible to obtain resins with a wide range of properties which are suitable for moulded articles.

A more recent development is to subject the pre-formed polyvinyl acetate to further chemical change.¹ Complete hydrolysis removes the acetate groups, leaving a polyvinyl alcohol (*Solvars*) ; by partial hydrolysis polymers of mixed functions are obtained with differing solubilities and viscosities. The hydroxylated compounds can be made to react with aldehydes (acetal formation) yielding *Formvars* from formaldehyde, *Alvars* from acetaldehyde, *Butvars* from butyric aldehyde. These products may be generalised in the formula



To a minor extent the aldehyde molecules may also form cross-links between the polyvinyl chains. Such polymers are utilised as lacquers, adhesives and for moulding. *Formvars* and especially *Butvars* are employed as interlayers in laminated safety glass for automobiles.

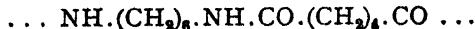
¹ See G. O. Morrison, *Chem. and Ind.*, 1941, pp. 309, 390.

Styrene, prepared from ethylene and benzene (see p. 457), is polymerised by means of heat, in some cases with the aid of an accelerator. For the structure of the chain see p. 876. The polystyrene or *distrene* thus obtained has the very low specific gravity of 1.05; it softens about 70° to 90° and is used in fluid form at 160° to 180° for injection moulding. Being to all intents and purposes a saturated hydrocarbon, the polymer is strongly resistant to corrosion and oxidising agents. Its exceptionally good insulating qualities are not lost even after immersion in water. For these reasons the main use of styrene polymers is in the electrical industry.

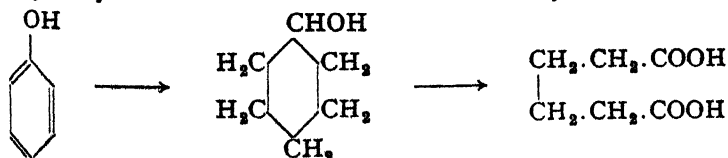
Polythene, polyethylene, was first made by Imperial Chemical Industries but is now also manufactured in the United States, where ethylene is obtained in huge quantities from natural and cracked gases. Its manufacture involves a new high-pressure technique. Polythene has extraordinary insulating properties combined with remarkable lightness.

Nylon, the first truly synthetic fibre, was developed by Carothers and his co-workers in America as a result of preliminary investigations carried out on polyesters, such as those prepared by the condensation of glycol with a dibasic acid (see p. 876). It was found that the threads formed by dipping a rod into the molten polyester were brittle and of low tensile strength; but that when they were subsequently cold-drawn to several times their original lengths they became tough and could then be tied into knots without breaking. The drawing process also greatly increased the lustre and tensile strength. An X-ray examination showed that the cold-drawn fibres, unlike the original filaments, gave a definite diffraction pattern, proving that the treatment had brought about a considerable degree of orientation of the molecular chains parallel to the fibre axis. This discovery proved later to be of fundamental importance for the production of Nylon threads.

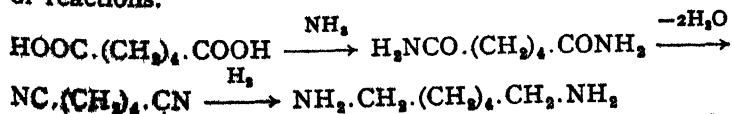
Nylon, also known as "66," was first synthesised in 1935. It is prepared by condensing hexamethylene diamine and adipic acid by heating them in an autoclave in the presence of stabilisers to control the molecular weight and viscosity of the final product. It is thus a polyhexamethylene-adipamide built up of recurring units of the structure



The raw material for the preparation is phenol, which is reduced catalytically to cyclohexanol and the latter converted by oxidation into adipic acid.

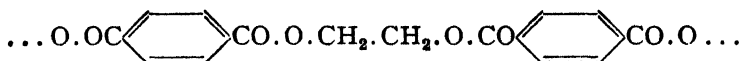


Hexamethylenediamine is obtained from adipic acid by the following series of reactions.



It is thus in a state suitable for storage and for the blending necessary to eliminate variations in individual batches. Nylon has a molecular weight of about 10,000 and melts at 263° . The latter figure is somewhat high for a thermoplastic resin, but resistance to heat is essential for a material which has to be submitted to washing and ironing. Spinning is carried out with the molten polymer at 285° in an atmosphere of nitrogen (it can also be effected with a phenol solution) and the newly-formed threads are by a continuous process cold-drawn to about four times the original length. The resulting filaments have a high tensile strength, elasticity and lustre. They can be made finer, stronger and more resistant to chemical action than natural silk, or in larger diameters for use in the manufacture of bristles, for the replacement of gut in surgical sutures, racquet strings, fishing lines and for a variety of other purposes.

Terylene, discovered by J. T. Dickson and J. R. Whinfield, is a new British thermoplastic which is now commercially available as a synthetic textile fibre. It is the polyester of ethylene glycol and terephthalic acid



Thermosetting Resins

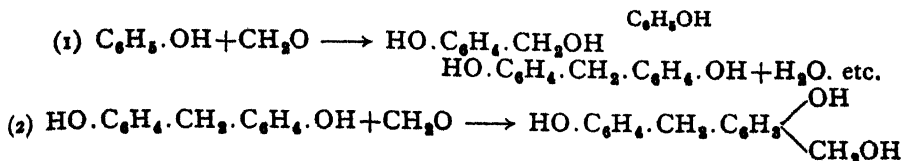
Resins of this type undergo polymerisation or condensation during treatment in the heated mould so as to form insoluble and infusible materials, which cannot be further reshaped by heat and pressure. In this group are the *bakelites*, *urea plastics*, and the *glyptals* or *alkyd resins*.

In these thermosetting resins the constituent long chains become cross-linked in all directions by shorter chains to give a rigid lattice arrangement. These cross-linkages depend for their formation on the use of tri- and poly-functional monomeric molecules. It is perhaps appropriate to stress again that a distinction is thus drawn between bifunctional monomers which yield thermoplastic resins and poly-functional monomers, which form resins of the thermosetting type.

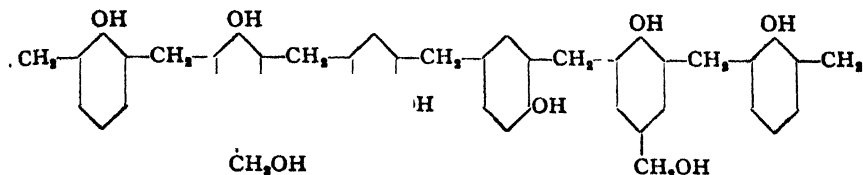
Although thermosetting resins cannot be remoulded, they have the advantage of being more resistant to solvent action and to high temperatures. They are made in two stages, and the final moulding process is a short heat treatment ranging from a few seconds to several minutes. With thermoplastic resins a longer period has generally to be allowed, in order that the mould may cool and its contents solidify.

Phenol-aldehyde plastics or **phenoplastics** of the *bakelite* type are made by condensing a phenol with an aldehyde, usually phenol with formaldehyde. The first stage is carried out at about 70° in the presence of a catalyst such as ammonia or sulphuric acid and using a copper or stainless steel still. Water eliminated during the reaction is removed

by distillation, and the fluid resin (*Novolak*) is run off and allowed to solidify. It is believed that the initial reactions are,



leading to a mixture composed of long chain molecules of irregular constitution and containing as yet uncondensed CH_2OH -groups, e.g.



Novolaks prepared by a short heating process are fusible and soluble. These are used for the manufacture of cements, varnishes and laminated materials.

In the second stage the powdered *Novolak* is mixed with fillers such as wood flour, which give a greatly improved product, and with colouring matters; it is then moulded under compression at a high temperature. Phenol is a polyfunctional reactant, having one para and two ortho positions open to attack, and during the final moulding further condensation occurs in which new methylene groups derived from the uncondensed CH_2OH -groups form cross-links between the molecular chains, giving a three-dimensional lattice.

By the exercise of careful control the first stage of the preparation is broken off while the resin (*Novolak*) has still the necessary fluidity under heat and retains sufficient chemical reactivity to yield a well-shaped rigid product at a higher temperature in the mould.

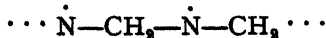
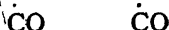
Certain other phenols such as *m*-cresol, which has also one para and two ortho positions available, may be used as starting material, but *o*- and *p*-cresols are only bifunctional and are not by themselves capable of forming a thermosetting resin.

The applications of the phenol-aldehyde plastics for moulded articles are too many to be described in detail. It may be noted, however, that they are used very successfully for the manufacture of gear wheels, not only for small-scale work but also in cement plants, steel rolling and paper mills, where with water as lubricant they have proved more silent and much cheaper in the long run than gears made of metal. A disadvantage of the phenolic resins is their dark colour, hence white or brightly coloured articles are made from other types such as the urea-formaldehyde plastics.

Urea or amino plastics are prepared from urea and an aldehyde often with the addition of thiourea. The first stage of the reaction is commonly carried out by dissolving urea in aqueous formaldehyde below 10°C ., and then effecting condensation at about 130° . Water is subsequently removed under reduced pressure, and the molten resin is run off. The product is comparatively colourless, and after being mixed with fillers (wood flour or cellulose pulp) and brightly coloured dyes it is used for the final moulding process, during which cross-links are formed between the molecular chains and the material becomes infusible and insoluble (*Beetle ware*). The primary condensation products have been identified as *monomethylol-urea*, $\text{NH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\text{OH}$, and *dimethylol-urea*, $\text{HOCH}_2\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}\cdot\text{CH}_2\text{OH}$. The problem of how such bifunctional compounds give rise to cross-linkages has not yet been finally solved, but is certainly complex. It is probable that the methylol derivatives lose water to give azo-methine ($-\text{N}:\text{CH}_2$) derivatives. Thus dimethylol-urea can yield the tetrafunctional product A, which can undergo addition polymerisation to give a cross-linked product such as B.



(A)



(B)

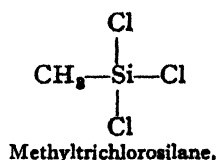
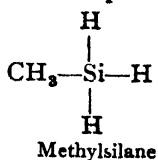
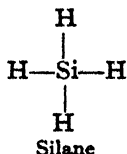
Glyptals or alkyd resins represent another type of synthetic resin obtained by the condensation of glycerol (glycol or mannitol) with an acid such as phthalic acid (isophthalic, tartaric, citric, succinic acid, etc.). The product forms a tough leathery mass at high temperatures which only becomes completely hard after prolonged heating and is therefore rarely used in a mould. Glyptals are employed in large quantities as bonding agents for asbestos, mica, etc., and other materials required to withstand high temperatures, such as brake linings and supports for heavy electrical windings. Unlike shellacs and the phenolic resins, which only form an external coating when applied to cotton and other fabrics, the glyptals penetrate into the pores of the material. Mixed plastics (*Paralacs*, *Bedesols*) of a different type are also made by combining glyptals with natural resins, *e.g.* copals, colophony, as well as with other synthetic resins and with drying oils. These are largely used for the manufacture of paints, lacquers and stoving enamels.

Organosilicon Polymers ¹

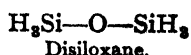
Organosilicon polymers with remarkable heat-resistant powers have recently been shown to be of great potential value and their commercial exploitation in many fields is expected. The polymers vary from viscous liquids such as "bouncing putty" to glasses resembling silica. In addition, some have extraordinary water-repelling properties.

¹ E. G. Rochow, *An Introduction to the Chemistry of the Silicones* (J. Wiley and Son, 1951).

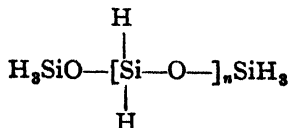
A systematic nomenclature is applied to the silicon compounds, according to which the simpler derivatives are regarded as derivatives of the silicon hydrides, *silanes*. For example :



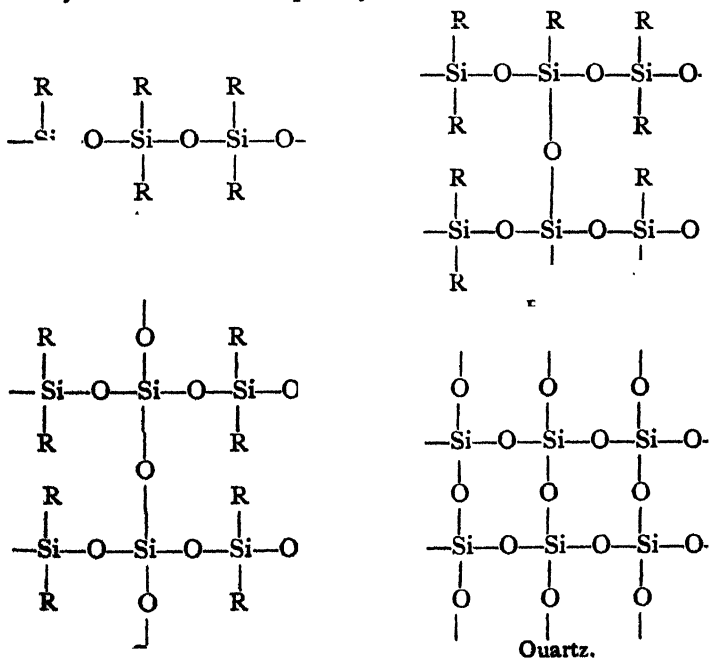
Compounds containing two silicon atoms are known as *disilanes* and if an oxygen atom is inserted between them the resulting compounds are *disiloxanes*.



Siloxanes often form long chains and may then be regarded as polymers of the following type :—

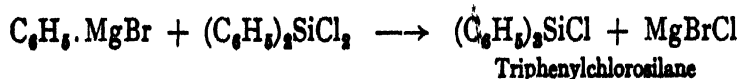


If the hydrogen atoms in these polymers are replaced by alkyl or aryl groups *polyorganosiloxanes* are obtained which contain the unit $-\text{RHSiO}-$ or $-\text{R}_2\text{SiO}-$, the latter being known as *silicones*. From these chain-polymers may be derived three-dimensional polymers, somewhat similar in structure to silica. In these, the cross-linkages are obtained by the use of incompletely substituted siloxanes.

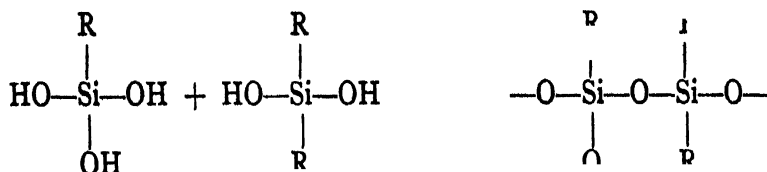


In type A all the silicon atoms are attached to two and only two oxygen atoms : in B some are attached to three oxygen atoms and in C to four. In quartz each silicon atom is linked to four oxygen atoms. The number of cross-linkages in a polymer will depend on the degree of substitution the degree of substitution will therefore govern the properties of the polymers such as solubility and fusibility. Other properties such as chemical characteristics will depend more on the nature of the substituents.

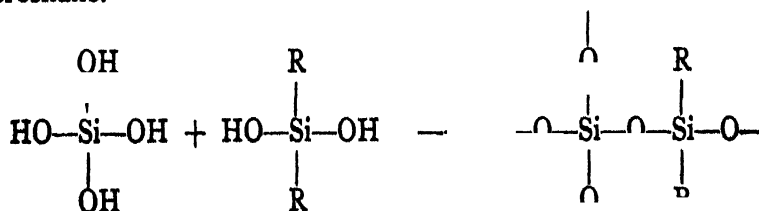
Thanks largely to the pioneer work of Kipping, methods are known for the preparation of organosilicon compounds. For instance, Grignard reagents react with silicon tetrachloride to give chlorinated silanes.



From these and similar chloro compounds polymers with cross-linkages are prepared. For example, polymers of the following type are obtained by hydrolysis of mono- and disubstituted chlorosilanes.



Another method is the hydrolysis of silicon tetrachloride and a dialkyl-dichlorosilane.



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